UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE
COMPANY, JOHN HANCOCK
VARIABLE LIFE INSURANCE
COMPANY and MANULIFE
INSURANCE COMPANY,

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

AFFIDAVIT OF BRUCE E. RODDA, Ph.D.

I, Bruce E. Rodda, hereby declare and say:

1.   I have been asked by Munger, Tolles & Olson LLP, on behalf of Abbott Laboratories, to provide the Court with expert testimony regarding the development of new pharmaceutical compounds, including without limitation, the statistical aspects of evaluating and interpreting the results of clinical trials in support of these developmental activities.

2.   I am the Principal of Strategic Statistical Consulting, LLC, a firm that provides statistical consulting to the pharmaceutical and biotechnology industries. I am also an Adjunct Professor of Biostatistics at the University of Texas.

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<u>Educational and Employment Background and Qualifications</u>

3.   I received a B.A. in mathematics from Alfred University, an M.S. and Ph.D. in Biostatistics from Tulane University, and an M.B.A. from Fairleigh Dickinson University.

4.   After receiving my Ph.D., I spent more than 30 years in the pharmaceutical industry, working for Eli Lilly, Merck, Ayerst Laboratories, Bristol-Myers Squibb, Schering-Plough, PPD Development, and Pharmacia. At Eli Lilly, I was the senior statistician in Lilly's clinical research efforts. In that capacity, I participated in the design and analysis of clinical trials and was the company's representative to the FDA regarding statistical matters. I left Eli Lilly to join Merck, where I was in charge of clinical biostatistics and research data systems for all Merck's development studies that were conducted outside the U.S. I left Merck as Senior Director of this organization. I then went to Ayerst Laboratories, where I led Technical Operations for the company, which included statistics, data management, clinical operations (clinical trial field monitoring staff), and clinical systems.

5.   I next joined Bristol-Myers Squibb, where I was responsible for all statistics and data management activities for the company on a global basis. I also had responsibilities for clinical operations prior to Squibb's acquisition by Bristol-Myers. In my next position, at Schering-Plough, I served as Vice President of Research Administration, a role in which I directed several functions, among them being statistics, data management, medical writing, project management, research systems, clinical operations, and finance. I then joined PPD Development as Vice President for

Operations, Americas. In this position, I directed statistics, data management, and clinical operations for all North and South American operations for a large contract research organization.

6.   After a short period on the faculty of Texas State University, I returned to the pharmaceutical industry with Pharmacia, serving as head of Medical Development Strategy until Pharmacia's acquisition by Pfizer in 2003. In this position, I was responsible for the strategic, financial, organizational, and administrative operations of the global clinical development organization.

7.   During my career in the pharmaceutical industry, I held academic appointments at Indiana University, The University of Illinois, The Rockefeller University, and Texas State University.

8.   In 2003, I established Strategic Statistical Consulting, LLC and joined The University of Texas as an Adjunct Professor of Biostatistics where I teach a course in clinical trials. Strategic Statistical Consulting assists pharmaceutical and biotechnology companies in the design and strategic considerations of clinical trials. This includes planning and developing protocols, experimental design, and regulatory strategies. The company also consults in the planning and evaluation of statistical analyses and clinical study reports, and represents their clients in interactions with regulatory agencies, such as the FDA.

9.   I am an elected Fellow of the American Statistical Association; I have been awarded a Commissioner's Special Citation by the Commissioner of the Food and Drug Administration; and I was honored with a Career Achievement Award by the Pharmaceutical Research and Manufacturers of America.

10.   I am the author or co-author of approximately 70 scientific publications and have presented approximately 50 papers at scientific meetings. Attached hereto as D's Exhibits BN and BR, respectively, are true and correct copies of the two expert reports that I prepared in this matter. True and correct copies of my current C.V., a summary of my industrial experience, and a list of selected scientific publications are attached as Exhibits 1, 2, and 3, respectively, to D's Exhibit BN.

11.   I am being compensated on an hourly basis for the work that I perform in this matter at the rate of $350 per hour plus expenses. My compensation is unrelated to the outcome of this litigation.

<u>Tasks</u>

12.   My opinions in this matter are based upon my own experience, generally accepted statistical theory and practice, information and materials available in the public domain (including, but not limited to, information from the United States Food and Drug Administration's ("FDA") website and the European Medicines Agency ("EMEA") website), and upon testimony and materials obtained in discovery in this action. In addition to other materials, I have reviewed the reports and deposition testimony of Dr. Barry I. Gold and Dr. William R. Fairweather, expert witnesses retained by Hancock in this matter.

13.   I have been asked to opine on certain opinions and statements set forth in the affidavits of Dr. Gold and Dr. Fairweather, filed by Hancock on January 28, 2008, and on the expert reports that Dr. Gold and Dr. Fairweather prepared in this matter. My opinions in this regard are set forth below and in the two expert reports that I previously submitted in this matter, true and correct copies of which are attached hereto as D's

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Exhibits BN and BR. I have intentionally not included in this affidavit all of the opinions set forth in my expert reports, since Dr. Gold and Dr. Fairweather have not included in their affidavits all the opinions that were included in their respective expert reports.

14.   In paragraphs 15 — 45 below, I principally address the opinions expressed by Dr. Gold and Dr. Fairweather regarding the statistical issues associated with clinical development generally and Abbott's M99-114 clinical trial of ABT-594 in particular. In paragraphs 46 — 58 below, I address other opinions expressed by Dr. Gold and Dr. Fairweather.

<u>Statistical Issues Regarding Clinical Development and the M99-114 ABT-594 Trial in Particular</u>

<u>General Considerations</u>

15.   A "successful" trial is one that is definitive, not necessarily one that is supportive of the desired result. Although a sponsor would like each of its trials to be supportive of the ideal outcome of bringing a new product to the market, it also does not want to invest in a product that will not be safe and effective, nor expose patients in clinical trials to an experimental therapy unnecessarily. Therefore, a clinical trial that provides a conclusive result, even if the outcome differs from that desired by the sponsor, may be considered a "successful" trial. The term "negative" may also have several meanings when referring to the results of a clinical trial. Two such interpretations might be that a study is inconclusive or that a study is conclusive, but does not support the desired outcome. These are very different cases.

16.   The conventional approach to evaluating a comparative clinical trial is to assume, before the study begins and data are obtained, that the treatments under investigation do not differ in their response. This is referred to in statistical terminology

as the "null hypothesis". The study is then conducted with the objective of collecting information that will refute this hypothesis if the experimental treatment is, in fact, superior to the control treatment. If a substantial difference favoring the experimental treatment is observed when the study is completed, the conclusion would be that the experimental treatment is superior to the control. In the context of Abbott study M99-114, this means that Abbott designed Study M99-114 to have a high likelihood of producing results that would support the conclusion that ABT-594 was superior to placebo if, in fact, ABT-594 was truly superior.

17.   Attached hereto as D's Exhibit 795 is a true and correct copy of the clinical study report (CSR) for Study M99-114. The results of M99-114 did in fact provide a substantial, statistically significant difference between each of the three doses of ABT-594 and placebo with respect to the primary variable (Likert pain scale), confirming the superior efficacy of each of the three doses of ABT-594 compared with placebo. While the affidavits of Drs. Gold and Fairweather discuss other aspects of the study, neither individual questioned that the M99-114 trial was conclusive in demonstrating that ABT-594 was superior to placebo with respect to the primary efficacy variable, despite a sample size that was somewhat less than originally planned.

18.   The results of a clinical trial are analyzed to provide a basis for reaching conclusions. When the study is completed and the data have been unblinded, the statistical team will perform a complete statistical evaluation of the study results based on a plan that was designed prior to unblinding the clinical data. This plan for the statistical analysis will sometimes be included in the body of the protocol or may be written as a standalone document for complex studies. If a standalone SAP is written, it is often

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appended to the protocol. The statistical analysis will be performed in concert with clinical experts and will be extensive.

Power and Sample Size:

19.   Every clinical trial is different and the outcome of each clinical trial is unpredictable. If the identical trial were conducted many times, the results would differ each time for a variety of reasons. In addition to the uncertainty caused by random variation, other factors affect the confidence we have in the inferences made at the conclusion of a study. Some of these factors are the variability of the basic measurement, the size of the true difference between the experimental treatment and control (which is unknown and must be estimated from the study), the probability with which one wishes to detect a true difference of a certain magnitude if it exists (power), the risk one is prepared to take in declaring a true difference exists when it does not (Type I, or alpha, error), and the number of patients participating in the study.

20.   For example, to estimate the sample size for Protocol M99-114, Abbott used information from Protocol M98-833. That study suggested that a meaningful difference would be 11.4 units on a 100 point Likert scale with an associated standard deviation of 24.4 units, yielding a standardized difference (or treatment effect) of 0.46. Abbott utilized this standardized effect size, a power (or probability of getting a statistically significant outcome if the anticipated difference was real) of at least 0.8, and an acceptance of a 5% risk of falsely declaring ABT-594 superior to placebo, resulting in a planned sample size of approximately 80 patients in each group.

21.   Power is a concept that is only relevant for planning a clinical trial and is of little value in the interpretation of the results of a study. The reasoning behind this is

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as follows.   Under assumptions to be explained later, power is the probability of obtaining a statistically significant outcome in a study to be conducted.   Once the study has concluded, the result is either statistically significant or not statistically significant, and the probability of statistical significance is no longer relevant.   For example, consider the probability of throwing a "3" with a single die.   Before the die is tossed, the probability of getting a "3" is 1/6.   Once the die has been thrown, the result was a "3" or was not a "3".   The probability of getting a "3" is no longer a factor.

22.   Organizations sponsor clinical trials because they believe that their experimental treatment will have a clinically important difference over the standard treatment or a negative control.   When a sponsor commits to performing a clinical trial, the sponsor wants to minimize the likelihood that the study will be inconclusive.   Said differently, if the new treatment has a clinically important effect of Δ, the sponsor wants the study to have a high likelihood (or power) of demonstrating that effect with a "statistically significant" result.   That is, the sponsor does not want the study to result in a conclusion of "ineffective" or "inconclusive" if the product really is superior to the control.   Intuitively, because a larger trial provides more information than a similar smaller trial, a larger trial will be more likely to be conclusive than a smaller trial. Because clinical trials are very expensive, it is critical that studies be designed with the proper number of patients to satisfy their goals.   Too many patients will result in unnecessary exposure of patients to experimental treatments and will be unnecessarily expensive.   Too few patients, on the other hand, may result in an inconclusive study with the potential need to repeat it.   For these reasons, a clear strategy must be followed for determining the number of patients required in a clinical trial.

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23.   Four basic factors influence the size of a clinical trial, (1) variability (or noise); (2) the difference between the experimental treatment and the control that is clinically important; (3) the risk of incorrectly concluding the new treatment is superior when it is not; and (4) the risk of incorrectly concluding that a clinically important effect is absent. I address each of these four factors in turn below.

24.   Variability – If a treatment effect is associated with very small variability (i.e. the treatment effect is very consistent), few subjects would need to be evaluated in a clinical trial to have confidence regarding any decisions made about the particular effect of interest. In contrast, if the effect is quite variable or inconsistent (i.e., there is a lot of noise), conclusions based on the information provided by the same few patients would be less convincing. To provide the additional information necessary for similar confidence in the two cases, more patients must be evaluated when there is greater variability. For any scientific measure, precision increases and the likelihood of error decreases with additional information. In the clinical trial context, this information corresponds to a decrease in variability and/or an increase in the sample size.

25.   Clinically Important Difference between the Experimental and Control Treatment - The second factor that influences the size of a study is the difference between the experimental treatment and the control that is clinically important. If the true (but unknown) difference between the comparative agents is real, but very small, the study will require a large number of patients to provide adequate evidence to conclude that the true difference is not zero as stated in the null hypothesis. On the other hand, if the sponsor believes that its new product is superior to the standard by a substantial margin,

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fewer patients will be required to obtain a statistically significant result if the true difference between the two treatments is large.

26.   Risk of a False Positive Conclusion - The third consideration influencing the size of a clinical trial is the probability of falsely concluding the new treatment is superior when it is not. Consider that even if the experimental treatment and control treatment had inherently identical effects, the results of any specific study could randomly favor the experimental treatment to a degree that the (incorrect) conclusion would be that the experimental treatment is superior to the control treatment. The probability of making this type of mistake is also called a Type I error or alpha error (also referred to as the level of statistical significance) and is chosen before the study begins. At the conclusion of the study, the null hypothesis is tested against this alpha error standard (e.g. $p < 0.05$), and if the results of the study are more extreme than would be expected if there were no true difference, the result would be called "statistically significant (at the $p < 0.05$ level)" and the conclusion would be that the experimental treatment is effective. The probability of making this conclusion in error would be 0.05 (or 1/20) in this example. The Type I error is usually set at 0.05 (or 5%) and this is a standard recommended by the FDA and other regulatory agencies. Hypothesis tests routinely use this cutoff as the definition of "statistical significance". In the present study (M99-114), the alpha level was chosen to be 0.05 and was specified in the protocol. While not addressed in either Dr. Gold's or Dr. Fairweather's affidavits, at the conclusion of Study M99-114, the results of comparing each dose of ABT-594 with placebo were "statistically significant" ($p < 0.05$), implying that each dose is truly more effective than placebo in reducing pain in diabetic neuropathy patients.

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27.   Risk of a False Negative Conclusion/Power – It is also possible to incorrectly conclude that a clinically important effect is absent.   Suppose that the experimental treatment is truly superior to the control treatment by, say Δ units.   As mentioned above, the results of any study are unpredictable, and even though the experimental treatment is, in fact, superior to the control treatment, the outcome of a particular study might result in a difference that was quite small, just by chance. In that case, the test of the null hypothesis would not be rejected (that is p would be greater than 0.05), and the incorrect conclusion would be that the experimental treatment is not superior to the control treatment. This type of error is referred to as Type II error or Beta error. The probability of correctly concluding that the experimental treatment is superior to the control is one minus the probability of incorrectly concluding the treatment is effective. The probability of correctly concluding the experimental treatment is superior is termed "power". Sponsors and investigators usually want this probability to be quite high and often select sample sizes that will provide 80% power. In study M99-114, the planned power was 80% power.

28.   The relationships among the various factors contributing to the estimation of the sample size may be made clearer by considering the following equation:

$$ n = \frac{2(z_{\alpha/2} + z_{\beta})^2 \sigma^2}{\Delta^2} $$

where: n is the sample size in each treatment group and

$z_{\alpha/2}$ is an index of the risk of a false positive –
the higher $z_{\alpha/2}$, the lower the risk (1.96 in Study M99-114)

z_{β} is an index of the risk of a false negative –

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the higher z_β, the lower the risk (0.84 in Study M99-114)

σ is the standard deviation – the measure of variability ($\sigma = 24.4$ from Study M98-833)

Δ is the difference the study is designed to detect ($\Delta=11.4$ from Study M98-833) (Note that $\Delta/\sigma =0.46$ is the standardized treatment effect Study M99-114 was designed to detect).

Note that the z-values above are values of standard normal deviates and are indexes of the probabilities; they do not represent the actual probabilities.

29.   The sample size for the Protocol M99-114 was estimated using a standard statistical approach for the comparison of two means. While there are usually several choices that may be appropriate for estimating the sample size in any clinical trial, the procedures used in this study were consistent with good statistical practice and the sample size was appropriate for detecting the pre-specified standardized treatment effect of 0.46 in the primary variable with 80% power at an alpha level of 0.05. Neither Dr. Gold nor Dr. Fairweather has challenged Abbott's calculation of the sample size for protocol M99-114.

30.   It should be understood that just because a sample size has been chosen which appears to provide 80% power, it does not imply that there is an exact 80% chance that a given trial will be successful. As stated above, power is a concept that is only relevant for planning a clinical trial and is of little value in the interpretation of the results of a study.

31.   Even if the planning has been appropriate and the calculations are correct consider the following points.

- The assumptions used to estimate the sample size are approximations. The estimate of variability used in the calculation of sample size is derived

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from previous experience, often in a different environment than the given study. The variability that will actually occur in the planned study may be greater or less than used in the power calculations. In these hypothetical situations, the power would be lower or higher than anticipated.

- The true difference between the treatments is unknown and the study may result in a higher or lower difference than that used to estimate the sample size. A greater difference results in greater power; a lesser difference results in reduced power.

- The new treatment may not actually be superior. (In fact, if a study correctly results in this conclusion, the study has not been a failure. The study has reached the correct conclusion, even though it was not the conclusion that was desired.)

- Even if the new treatment is superior, the difference actually seen in a particular study may not be conclusive, just by chance.

32.   Dr. Gold correctly notes at paragraph 60 of his affidavit that "there are no formal standards for the power of a study". The concept of power as it relates to estimation of sample size is a quantifiable risk chosen at the discretion of the sponsor. Neither "power", nor "statistical significance" is associated with the validity of a study. The validity of a study is dependent on its design and implementation, not on the selection of any particular power. Two studies of the same design but of different sizes will both be equally valid if they are properly designed and executed. The larger study will provide more information and precision regarding the conclusions than the smaller

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study, but they can be equally valid. The validity of a study does not diminish simply because the power of the study is reduced. Dr. Gold's suggestion at paragraph 60 of his affidavit that a trial must "'reach 80% power' in order to be considered statistically valid" is baseless and incorrect. For the reasons discussed above, it is inappropriate to use the standard of 80% power as an index of statistical validity.

33.   For similar reasons, Dr. Fairweather's references at paragraphs 14 and 37 of his affidavit to the supposed possibility of the M99-114 study being "underpowered" is inappropriate. It is correct that under the assumptions that Abbott used to estimate the power of M99-114, terminating enrollment before 320 patients were enrolled would reduce power below 80%. However, the term "underpowered" is an opinion and is not a scientifically defined term. As stated above, power is a risk chosen by the sponsor. It is not uncommon for a sponsor to assume a potentially greater risk of a false negative when enrollment is below expectation. Such a study may have lower power than originally planned, but would not necessarily be "underpowered". In the case of the M99-114 trial, as discussed below, Abbott did realize that there would be lower-than-expected enrollment and that the power of the trial could possibly be lower than 80%, all other things being equal. However, as is also discussed below, Abbott calculated that the power of the trial, even with smaller enrollment (266 patients instead of 320), would remain approximately 74%. Thus, even assuming both the variability and treatment effect were the same as Abbott hypothesized they would be in advance of the trial, Abbott could assume in March 2001 that there was still approximately a three-to-one likelihood that the trial would result in a statistically significant treatment effect and that the trial would be successful in achieving its stated goals. Even assuming a reduction in

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sample size to the smallest number of patients included in Abbott's primary analysis (225), the power of this study would be approximately 67% and would mean that there would be a two-to-one likelihood that the study would be successful. Indeed, Dr. Fairweather, at paragraph 41 of his affidavit, notes that the power of the study as of March 12, 2001, and using the intent-to-treat analysis required by Abbott's Protocol for the M99-114 Trial, would have been "approximately 70%". These are still very favorable odds.

34.   The "power" of the study refers directly to the probability that the study, as designed, will find the pre-specified clinically important difference to be statistically significant at a pre-specified risk of a false positive outcome (declaring an ineffective drug to be effective). The "power" of the study is not the probability of failing to detect a true, pre-specified, difference; it is the probability of actually detecting that difference. Moreover, contrary to Dr. Gold's statement at paragraph 59 of his affidavit, the "power" of a study is not the probability that the test will detect a "true difference" between two groups; rather, it is the probability that the test will detect a "true difference *of a certain, pre-specified magnitude*" between two groups. As discussed above, the power of a study and the size of the difference that the sponsor wishes to detect by that study are inextricably linked. It is the sponsor, through the project team (and often following discussions with the FDA), who defines the pre-specified difference and is most interested in the outcome.

Results and Conclusions of the M99-114 Study

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35.   At paragraph 37 of his affidavit, Dr. Fairweather incorrectly refers to the M99-114 trial as "prematurely terminated". The M99-114 trial was not "prematurely terminated". Abbott decided to halt *enrollment* of patients into the trial prior to achieving the pre-specified number of 320 subjects. Abbott continued all enrolled patients to the planned conclusion of the trial. It is important to distinguish between stopping enrollment before the target sample is acquired but then continuing enrolled patients to completion, versus completely halting the study at a particular point in time. Dr. Fairweather fails to make this important distinction.

36.   Dr. Fairweather appears to suggest at paragraphs 38 and 42 of his affidavit that Abbott erred in assuming as of March 2001 that data based on all subjects who enrolled in the study, including the subjects who did not complete the trial, should be utilized in estimating the effective power of the study. Had Abbott used this approach, they would have effectively assumed that the only valuable data was from available from the 138 patients who completed the entire study. Good scientific practice dictates that all available information be used in any analysis. Discarding useful information from patients who participated in, but did not complete, the study would not have been consistent with good clinical practices, industry standards, and regulatory guidances.

37.   Both the International Conference on Harmonization (ICH) and the U.S. Food and Drug Administration (FDA) recommend using as complete a dataset as possible for evaluating both safety and efficacy. Any patient that can be evaluated for efficacy should be included in the primary analysis. The analytic approach Abbott proposed for protocol for study M99-114 is consistent with the intent of this guidance. In fact, the protocol states that "all subjects receiving at least one dose of study drug with at least one

diary-based baseline and at least one post-baseline pain assessment for the diary-based

Pain Rating Scale will be included in the intent-to-treat analysis." The description of this

dataset is included in the protocol and was defined before the study was begun. This

dataset is consistent with ICH E-9 (Statistical Principles for Clinical Trials) which

describes such a dataset as being "as complete as possible and as close as possible to the

intention-to-treat ideal of including all randomized subjects." The clinical study report

for Protocol M99-114 includes 225 of the 266 patients randomized to treatment in the

primary efficacy analysis; all 266 patients are included in the safety analysis.

38.   Patients withdraw from clinical trials for many reasons. Some are random

and do not influence or bias the conclusions. However, patients may withdraw from

clinical trials for two primary reasons that may be related to the treatment they receive -

the adverse events they experience are such that they no longer wish to participate in the

study or the treatment they are receiving is insufficiently effective to support their

continued participation in the study. In either case, patients who withdraw from a study

provide valuable information regarding the safety and efficacy of the product under

investigation. Excluding patients from the analysis of clinical trials can substantially bias

the conclusions reached. It is for this reason that both ICH guidelines and the FDA

recommend using all patients with valuable data in the analysis of safety and efficacy,

including patients that do not complete the trial. In reviewing the documentation of

Abbott's deliberations prior to terminating enrollment, there was never a reference to

using less than all evaluable patients in the appropriate analyses. For these reasons, the

suggestion in paragraph 38 of Dr. Fairweather's affidavit that only those subjects who

"completed the trial" should have been considered for evaluation or included in power

calculations is both scientifically inappropriate and inconsistent with ICH and FDA standards. To use only the 137 ("138" in Dr. Fairweather's affidavit) completing patients as Dr. Fairweather suggests would not be consistent with good scientific practice, would bias the results in favor of ABT-594, and would not be acceptable to the regulatory and scientific community. ICH guidelines and the FDA suggest that all relevant information be used in the analysis; patients who withdraw cannot be considered "unusable" for either safety or efficacy. In addition, if one were to accept Dr. Fairweather's contention regarding usability, the original sample size of 320 patients would need to be increased by a factor of 266/137 (1.94), to a total enrollment of 621 patients to net 320 "usable" patients.

39.   When patients who do not complete a trial are included in the intent-to-treat analysis, data are often imputed for their observations that are missing. In this case, patients with imputed data may be treated in the same manner in the analysis as patients with complete data. Given the ICH guidelines and the FDA recommendation referenced above that all patients with valuable data be included in the analysis of safety and efficacy, both the ICH and the FDA anticipate that imputed data may be submitted in support of the analysis and conclusions of a clinical trial. Although there is more information available from patients who complete a trial than for those who do not, the use of imputed data is common in the statistical analysis of clinical trials.

40.   Documents relating to internal meetings at Abbott suggest that (1) Abbott became aware at some point that they would not meet the enrollment goals in the planned enrollment period for Study M99-114; and (2) conducted an analysis by which Abbott estimated the expected power of the study given certain assumptions. During the period

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preceding Abbott's decision to terminate enrollment, several activities took place in an effort to determine the impact of the smaller-than-expected enrollment on the probability that the study would satisfy its goal of distinguishing ABT-594 from placebo. In addition to efforts targeted at improving enrollment, Abbott evaluated the effect of smaller sample sizes on the probability (power) of detecting their predefined standardized treatment effect of 0.46. This was done in a fully blinded manner and assumed that all patients would be evaluable for efficacy. This activity focused on the following question: if the study concludes with a reduced number of patients, what is the probability (power) of detecting (finding statistically significant, $p<0.05$) the proposed treatment effect of 0.46 between ABT-594 and Placebo? An example of the power considerations of this evaluation is contained in a memo from Mr. James Thomas to Ms. Rebecca L. Brown on 9/28/2000 in preparation for a meeting on the topic. This table is reproduced in part below.

Option	Sample Size	Effect	Power
1	20	.46	0.29
2	25	.46	0.36
3	30	.46	0.42
4	35	.46	0.48
5	40	.46	0.53
6	45	.46	0.59
7	50	.46	0.62
8	55	.46	0.67
9	60	.46	0.71
10	65	.46	0.74
11	70	.46	0.77
12	75	.46	0.80
13	80	.46	0.82

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Entries in this table include possible sample sizes (per group), the hypothesized treatment effect Study M99-114 was designed to detect (0.46) and the power to detect this difference for each sample size. It can be seen from this table that the actual number of patients at the termination of enrollment (266 or about 65 per group) would provide 74% power to detect the hypothesized 0.46 treatment effect (compared with an initial power of at least 80% as cited in the protocol). This activity provided Abbott with a full understanding of the probabilities of Abbott's detecting their chosen effect for several smaller sample sizes. However, if the true treatment effect was larger than 0.46, the probability of finding this larger difference with the reduced sample size would increase.

41. It is common in clinical trials for actual enrollment to be less than planned. The only risk of stopping enrollment in a study with fewer patients than planned (as it relates to power) is that the treatment difference between the experimental agent and the control agent may not be statistically significant. In these cases, the sponsor may accept that the study's power to detect the originally hypothesized difference may be lower than used in estimating the study's size. There are several strategic considerations that may affect the sponsor's decision. Extending a study for an additional year, for example, to acquire the planned sample size may increase the cost to an unacceptable degree or expose the product to a new competitive agent such that the higher risk of extending the study may be unacceptable to the sponsor. In addition, after the study has begun, factors such as safety considerations with the new treatment or the introduction of a new competitor may require that the treatment under study possess a larger superiority over the control treatment than was originally planned. In this case, a reduced sample size

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may be consistent with a comparable, or perhaps greater, power than originally planned, since larger effects require smaller sample sizes.

42. The M99-114 clinical study for ABT-594 was designed to enroll 320 patients. Despite prolonging enrollment and investigating methodologies for increasing patient enrollment, enrollment was terminated after enrolling 269 patients. These patients were uniformly allocated among the four treatment groups according to the randomization schedule. The study was not terminated prematurely; the study was run to conclusion, either to the point a patient withdrew or to the scheduled final visit for each patient.

43. While the sample size of 269 patients for the M99-114 trial was somewhat less than the planned sample size, completing studies with fewer than the originally planned number is common, especially for larger studies such as the M99-114 trial, since anticipated enrollment is often more than what is actually achieved in clinical trials. Moreover, in the case of the M99-114 trial, the total actual enrollment was approximately 83 - 84% of the original enrollment goal.

44. Although Abbott terminated enrollment before reaching the target of 320 patients, Abbott carefully evaluated the possible outcomes of the study based on the reduced sample size and concluded that the reduced power associated with the originally hypothesized treatment effect was acceptable. Referring to the table above, Abbott knew that its power to detect their original hypothesized treatment effect of 0.46 would be approximately 74%, rather than the planned 80%. Viewed somewhat differently, while the initial plan had an 80% power to detect a treatment effect of 0.46, the actual intent-to-treat sample of 225 patients (Clinical Study Report, Table 11.4a) had an 80% power to

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detect a treatment effect of 0.56. Since the actual differences observed between the active treatment groups and the placebo group were all in the range of 0.8 to 0.9 units on the 11 point Likert scale (and were all statistically significant at the $p<0.05$ level), the study clearly had adequate power to address the primary objective of the study, and the study should be considered conclusive (successful) in this respect.

45.   Although Abbott did not know the margin by which ABT-594 would be superior to the control when Abbott decided to terminate enrollment in this study, that margin was substantially larger than originally anticipated. This difference was manifested in results that were statistically significant, rendering the question of adequate power (i.e. the probability of obtaining a statistically significant result) moot. Although both Dr. Gold and Dr. Fairweather comment regarding study M99-114, neither questioned that the study was conclusive in demonstrating that ABT-594 was superior to placebo with respect to the primary efficacy variable, despite a sample size that was somewhat less than originally planned.

Back-Up Compounds

46.   Dr. Gold is incorrect in stating at paragraph 35 of his affidavit that "pharmaceutical companies do not develop a back-up or replacement compound unless they have decided to terminate the compound under development, or, at least, have substantial doubts about the commercial viability of the compound already under development". To the contrary, in my experience, backup compounds are often developed concurrently with or slightly behind the lead compound(s). Major companies have backup strategies and often will inlicense or develop a family of compounds, one of which may be the lead and the others "backups". For example, simvastatin (Zocor®) was

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a "backup" for lovastatin (Mevacor®) and lisinopril (Prinivil®) was a "backup" for enalapril (Vasotec®). In both these cases, the earlier compound was a multi-billion dollar success – certainly not a potential failure as Dr. Gold contends. In fact, many companies have formal strategies regarding development of backup compounds. The benefit of backup compounds is not necessarily to salvage a failed compound, but to provide alternative, perhaps superior, compounds. This would provide positive options to the company even if the initial compound was positive by providing two compounds in the class or a candidate for out-licensing. Since backup compounds can benefit from the lessons learned from earlier compounds, they are often more successful than earlier compounds in development. Thus, I disagree with Dr. Gold's conclusion at paragraph 38 of his affidavit that the fact that Abbott was looking in 2000-01 at possible back-up compounds for ABT-594 was necessarily an indication that Abbott had "serious concerns" about "the viability and prospects for ABT-594". In my experience, the contemporaneous development of back-up or potential replacement compounds with the development of a lead compound is common and represents good strategic planning, not an indication of doubt as to the viability or prospects of the earlier compound.

47.   Dr. Gold suggests at paragraphs 33 and 35 of his affidavit that the terms "backup compound" and "replacement compounds" are synonymous. This is not correct. As discussed above, a backup compound is not necessarily developed as a "replacement" for an original compound. The development of backup compounds often begins even before much testing is done on an original compound and without the intent that the backup "replace" an original compound. The term "backup" in this context does not imply that the "backup compound" will be developed only if the original compound fails,

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or only to replace a failed original compound. To the contrary, it is not unusual for pharmaceutical companies to bring both the original compound and one or more backup compounds to market, not because of a perceived "failure" on the part of the original compound, but because of the drug sponsors' desire to offer more than one type of drug in the same general class to treat the same illness or condition.

General Considerations Regarding Adverse Events in Clinical Trials

48.   In Dr. Gold's affidavit at paragraph 68, he contends that uncomfortable adverse events are likely to slow enrollment. However, since a patient must be enrolled to experience the uncomfortable adverse event, this is unlikely to be an issue on the patient level. In most studies, prospective patients do not know nor speak with one another. Since neither they nor the investigator would ordinarily know what the patient is taking, increasing the rate of dropouts or decreasing the rate of enrollment for this reason would not be common. On the investigator level, the investigator must view the existence of uncomfortable adverse events as an ethical issue to justify blocking enrollment of potential patients or to justify enrolling them in a competing study. In such a case, the investigator has an obligation to inform both the sponsor and the IRB of his concerns. For studies with small numbers of patients on each treatment, this should not be an issue if the study is double blinded.

49.   Dr. Gold's discussion of clinical trials that experience a "high number of adverse events," at paragraph 73 of his affidavit, is misleading insofar as it implies that a high number of adverse events may suggest that the results of a study might be negative. A high number of adverse events may suggest only that a study has a high incidence of adverse events, not necessarily that the results will be negative. Adverse events are

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characteristic of pharmacologic agents. One purpose of clinical studies is to estimate the incidence of adverse events and to characterize their distribution in the population. It is not the intent of most studies to minimize the occurrence of a phenomenon that may be associated with the therapy under study. An important objective in any clinical trial is to characterize the adverse event profile in the population under study.

50.   Studies of serious illnesses usually have high incidences of adverse events and do not imply any likelihood that the study will be negative.

Blinded Information, Adverse Events, and the M99-114 Clinical Trial

51.   In my experience, and to the best of my knowledge, major pharmaceutical companies do not use blinded information to make decisions regarding the potential outcome of a double-blinded clinical trial with respect to the future development of a drug. I personally have never been able to draw conclusions regarding the adverse event profile of a drug based on the adverse events seen during a clinical trial before the unblinding of the trial's data, nor am I aware that any statisticians working in the companies in which I have been employed or for which I have consulted have ever done so. In addition, I have not been familiar with any other scientists including physicians, attempting to draw definitive conclusions or inferences regarding adverse events from a clinical trial before the data were unblinded. To draw conclusions or inferences from blinded data, one would have to rely on speculation.   In my experience, major pharmaceutical companies do not make decisions based on speculation about the possible results of clinical trials, nor do they rely on blinded data for their decisions.

52.   An adverse event profile can vary substantially from study to study, even for the same product and similar protocol designs. If an experimental agent has a unique

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adverse event, observing an excess of this event in a blinded summary can be misleading if the underlying patterns of adverse events confound an ability to distinguish active therapy from control on this basis. The risks of terminating an expensive study based on blinded information is a risk that most companies do not choose to take. The possibility of inconclusive or incorrect decisions, the loss of money and time, and the ethical issue of enrolling patients in an inconclusive study are all reasons against stopping a study prematurely based on blinded data.

53.   For example, consider a study that is designed to compare a placebo (P) with two doses (low – L and high H) of an agent that is thought to be associated with an increased incidence of headache. If the study were conducted according to the protocol and evaluated in an unblinded manner at the study's conclusion, the relationship between the treatments and the incidence of headache could be determined.

54.   However, if one attempted to use blinded results at an interim analysis to form a judgment regarding the relationship between headache and the three treatments, it would not be possible to distinguish among the following cases (among others): P=L=H, P=L<H, and P<L<H.

55.   Consider a specific example of the above issue where information from previous studies suggests a 10% incidence of headache associated with the agent and that P, L, and H are studied in a trial of 300 patients (100 per treatment group). Suppose an interim analysis was conducted when the study is 50% complete (i.e. 50 patients per group) and a headache incidence of 20 % was observed (i.e., higher than expected). A blinded review of the results at this point would be unable to distinguish among the following three cases: P=10, L=10, H=10; P=5, L=5, H=20; and P=0, l=10, H=20. Thus,

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the blinded review could not distinguish among the cases where all treatments were the same; L is similar to P, but H has a high incidence of headache; and the case where there is an increasing association of headache with dose. Blinded evaluation would not reveal any of these patterns and making decisions based on such a blinded interim analysis could be misleading. For this reason, blinded review of interim clinical trail data is not commonly performed.

Out-licensing

56.   Companies are continually evaluating and re-evaluating their product portfolios against their corporate objectives. Since few, if any, companies are capable of filling their development pipeline with compounds discovered internally, companies are regularly considering in-licensing candidates to augment their portfolio and out-licensing candidates that may not fit with their corporate strategy. Dr. Gold states at paragraph 90 of his affidavit that companies "out-license compounds that have run into difficulty in clinical trials". In fact, companies out-license compounds for many reasons, not only the negative reasons on which Dr. Gold focuses. Moreover, contrary to the implications of Dr. Gold's statements at paragraphs 90 through 93, compounds with the problems Dr. Gold describes are often poor candidates for out-licensing, since interest in such a candidate will be low for a compound that has already demonstrated significant problems.
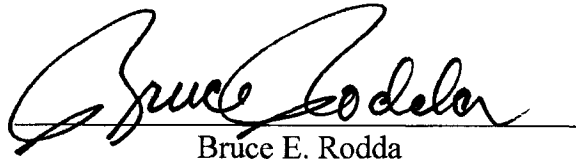
Phase I Trials

57.   Dr. Gold states at paragraph 43 of his affidavit that Phase I trials are designed, in part, to obtain preliminary evidence of efficacy. Because most Phase I studies are conducted in normal volunteers and not patients with the condition of interest,

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it is not usually possible to obtain evidence of effectiveness in Phase I studies. The exceptions to this generalization are Phase I studies involving oncology agents, where the adverse events often associated with such agents may make the administration of these agents to normal volunteers unacceptable. Many Phase I studies in oncology agents are therefore conducted in patients with the conditions of interest, providing an opportunity to obtain preliminary evidence of efficacy.

Target Profiles

58.   Dr. Gold's discussion of "target profiles" at paragraph 24 of his affidavit is overly broad and incorrect. Contrary to the implications of Dr. Gold's discussion, in my experience different companies define the term "target profile" in different ways. In addition, different companies use their target profiles or target product profiles for different purposes. A target product profile is, by definition, a target. Literally all drugs will "fall short" of the target in some way. This in no way indicates that they are not potentially valuable therapeutic advances. Nor does the fact that a drug does not meet its target profile in all respects necessarily mean that the sponsor of the drug will terminate development of the drug.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct and that this declaration is executed this __1⁵__ day of February, 2008, in Spicewood, Texas.

_____
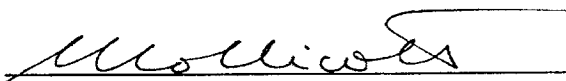Bruce E. Rodda

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ABBOTT LABORATORIES

Clinical Study Report No. R&D/01/171

A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful Diabetic Polyneuropathy

ABT-594/Protocol M99-114

31 July 2001

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.
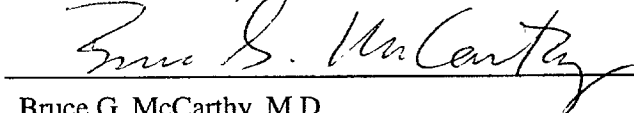
_____   _O1Aug01_
Marilyn J. Collicott   Date
Clinical Project Manager, Analgesia Venture
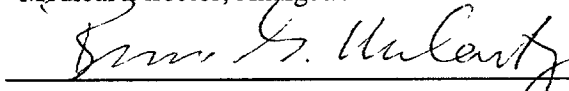
_____   _03Aug01_
David D. Morris, Ph.D.   Date
Assistant Director, Statistics

_____   _03 Aug01_
Bruce G. McCarthy, M.D.   Date
Medical Director, Analgesia Venture

_____   _03 Aug01_
Marleen H. Verlinden, Pharm.D., Ph.D.   FOR MARLEEN   Date
Vice President, Global Pharmaceutical Research and   VERLINDS, N
   Development Neurology/Urology

▭ **Abbott Laboratories**

ABT-594 (ABBOTT-165594)
Study No. M99-114
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1.0 Title Page

ABBOTT LABORATORIES
Clinical Study Report R&D/01/171

A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful Diabetic Polyneuropathy

ABT-594/Protocol M99-114

Development Phase:	II
Investigators:	Multicenter
Date First Subject Dosed:	24 April 2000
Date Last Subject Completed Dosing:	24 February 2001
Sponsor/Signatory:	Marleen H. Verlinden, Pharm. D., Ph.D. Vice President, Global Pharmaceutical Research and Development Neurology/Urology D42U, AP30 200 Abbott Park Road Abbott Park, Illinois 60064-6145 Phone: (847) 935-4096 Fax: (847) 938-1629
Report Date:	31 July 2001

This study was conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

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2.0   Synopsis

Name of Company: Abbott Laboratories	Individual Study Table Referring to Item of the Submission: not applicable (N/A) Volume: N/A Page: N/A	(For National Authority Use Only): N/A
Name of Finished Product: ABT-594 Hard Gelatin Capsule (HGC)		
Name of the Active Ingredient: Abbott-165594		

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful Diabetic Polyneuropathy		
Investigator(s): Multicenter		Study Center: Multicenter
Publication (reference): not applicable		
Study Period (years): Date First Subject Dosed: 24 April 2000 Date Last Subject Completed Dosing: 24 February 2001		Phase of Development: II

Objective:
The objective of this study was to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who had painful distal symmetric diabetic polyneuropathy, an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and ≥4 points on the site-based Pain Rating Scale (11-Point Likert Scale) at the Baseline Visit.

Methodology:
This was a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who had painful diabetic polyneuropathy. Approximately 320 subjects were assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg BID, or placebo for 49 days on an outpatient basis. Thirty-four sites were recruited in order to enroll approximately 320 subjects who met entry criteria for this study.

Prior to any study-specific procedures at the Screening Visit, an informed consent was signed by the subject and study eligibility determined.

Prior to study drug administration, subjects discontinued all analgesic medications (at least 7 days prior to the Baseline Pain Assessment Phase) and completed the 7-day Baseline Pain Assessment Phase. Following the Baseline Pain Assessment Phase, subjects who met entry criteria were randomized to a dose of study medication for 49 days (Primer and Treatment Phases). During the Primer Phase, subjects took BID doses of ABT-594 or placebo. Study drug was initiated at 75 µg BID. The dose was increased every 2 days in 75-µg BID increments until subjects were taking their assigned treatment dose (150 µg, 225 µg, or 300 µg BID). Following the Primer Phase, subjects entered the Treatment Phase (Day 8) and continued their treatment for a total of 49 days. During the Treatment Phase, subjects returned to the site for Treatment Visits I, II, III and IV (Days 14, 21, 35 and 49, respectively). Subjects were to complete diary-based assessments of their diabetic polyneuropathy pain each day from the 7 days prior to study drug administration (Baseline Pain Assessment Phase) through Day 49 of study drug administration. In addition, subjects underwent site-based assessments of their neuropathic pain at the Baseline Visit and at Treatment Visits I, II, III and IV. Subjects discontinued study drug administration after Treatment Visit IV and returned to the site for the Follow-Up Visit 7-10 days later.

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Methodology (continued):
During the Primer and Treatment Phases, subjects were allowed to take up to 3 grams of acetaminophen per day or up to 6 grams of acetaminophen per week (but were not allowed to take acetaminophen within 24 hours prior to a Treatment Visit).

Efficacy assessments included the Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), and Subject and Clinician Global Impression of Change. Safety assessment included physical examination, vital signs, electrocardiogram (ECG), clinical laboratory testing, and adverse event monitoring.

No. of Subjects Planned and Enrolled:	Treatment Group	Planned	Completed/Enrolled
Planned: 320	Placebo	80	51/65
Enrolled: 266	ABT-594 150 µg BID	80	40/65
Completed: 138	ABT-594 225 µg BID	80	30/69
Premature Discontinuations: 128	ABT-594 300 µg BID	80	17/67
	TOTAL:	320	138/266

Diagnosis and Main Criteria for Inclusion:
Adult males and females at least 18 years of age, who weighed ≤265 pounds and who were judged to be in good health based on medical history, physical examination with vital signs, laboratory profile, and 12-lead ECG, who had a diagnosis of diabetes mellitus (Type I or Type II), a diagnosis of distal symmetric diabetic polyneuropathy, good control (in the opinion of the investigator) of the their serum glucose for at least the last 3 months prior to the Screening Visit, and an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥4 points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit, and who met all other selection criteria were eligible for study participation.

Test Product, Dose and Mode of Administration, Batch Number:

Test Product	Dose (µg)	Mode of Administration	Drug Product Lot Numbers
ABT-594 75 µg HGC,	150, 225, and	Oral	58-293-AR
Formulation A-2	300 BID		61-312-AR

Duration of Treatment: 49 days

Reference Therapy, Dose and Mode of Administration, Batch Number:

Test Product	Dose (µg)	Mode of Administration	Drug Product Lot Number
Placebo for ABT-594 HGC	0	Oral	55-243-AR-01

Criteria for Evaluations:
Efficacy:
The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. Additionally, change from baseline to each scheduled evaluation was analyzed in a similar manner. The baseline pain score for the diary data was defined as the average of the last 7 pain scores prior to Day 1 of the study.

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Criteria for Evaluations (continued):
Efficacy:
Change from baseline to final and each evaluation was calculated for each of the following secondary efficacy variables:

- Site-Based Pain Rating Scale (11-Point Likert Scale)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health] physical component summary (PCS), and mental component summary (MCS).

The efficacy evaluations recorded at the Baseline Visit were used as the baseline score for efficacy evaluations assessed at the investigative site.

Pharmacokinetics:
Blood samples for ABT-594 plasma assay were to be taken from all subjects at Treatment Visits I and IV. For the subset of subjects who underwent additional pharmacokinetic sampling at Treatment Visits I and IV, values of AUC, C_{max}, and C_{trough} were determined.

Safety:
Safety was assessed by medical history, physical exam, vital signs, ECG, clinical laboratory testing, and adverse event monitoring.

Statistical Methods:
For all safety and efficacy analyses, the primary comparisons were between each ABT-594 dose and placebo.

Demographic and other baseline characteristic variables were analyzed to assess the comparability of the treatment groups.

The primary and secondary efficacy variables, including change from baseline diary- and site-based pain ratings were analyzed by using appropriate parametric and nonparametric methods. The final global evaluation scores, (Subject and Clinician) were compared using Cochran-Mantel-Haenszel methodology.

Dose response for ABT-594 was explored, with and without placebo included. Other efficacy analyses were performed as appropriate.

Treatment-emergent adverse events were summarized by body system and COSTART term and compared using Fisher's exact test.

Mean change from baseline to minimum, maximum and final values were summarized for clinical laboratory, vital sign and ECG data. Additionally, clinical laboratory data identified as below or above limits were flagged in the data listings. Furthermore, laboratory results which satisfied the criteria for limits for statistical analysis were identified.

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Summary/Conclusions:
Efficacy Results:
ABT-594 at 150, 225, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. Statistically significant linear dose responses were observed in the model that included the placebo treatment group for mean change from baseline to final for the average diary- and site-based Pain Rating Scale scores,

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to the subjects in the placebo treatment group.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline to final in SF-36™ Health Status Survey, a statistically significant improvement was observed for the ABT-594 225 µg BID treatment group in the physical component summary compared to the placebo treatment group. However, statistically significant worsening was observed for the ABT-594 300 µg BID treatment group in the mental component summary compared to the placebo treatment group.

Pharmacokinetic Results:
At the time of this report, the pharmacokinetic analyses were incomplete. Results from the pharmacokinetic analyses will be presented in a separate report.

Safety Results:
Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91% of subjects receiving ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

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Safety Results (continued):

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg and 300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time and individual clinically significant for laboratory evaluations, vital signs, ECGs, and physical examinations, were unremarkable for all treatment groups.

Conclusions:

ABT-594 at 150 µg, 225 µg, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to subjects in the placebo treatment group.

Date of Report: 31 July 2001

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4.0 List of Abbreviations and Definitions of Terms

List of Abbreviations

ABT-594	[(R)-5-(2-azetidinylmethoxy)-2-chloropyridine] or Abbott-165594
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
CMH	Cochran-Mantel-Haenszel
DNA	Deoxyribonucleic acid
EDTA	Edetic acid
HGC	Hard gelatin capsule
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward
MCS	Mental component summary
nAChR	Nicotinic acetylcholine receptor
NCR	No carbon required
NPRO	New Product Research Order
OC	Observed cases
PCS	Physical component summary
SEC	Soft elastic capsule
SF-36™	Short Form-36 Health Status Survey
SSRIs	Serotonin-specific reuptake inhibitors
TENS	Trancutaneous electrical nerve stimulation

Terms

Hemoglobin A_{1c}	Glycosolated hemoglobin
NOMAD®	A data management system

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5.0   Ethics

5.1   Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that approval be obtained from a research committee (e.g., Institutional Review Board [IRB], Independent Ethics Committee [IEC]), prior to participation of human subjects in research. The investigator obtained a duly constituted IRB/IEC review and approval of the protocol, informed consent form and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects). Abbott Laboratories received documentation of the study approval, the signed signature page from the study protocol, a signed Abbott Financial Disclosure form, subject informed consent document, a current investigator curriculum vitae, a signed Food and Drug Administration (FDA) Form 1572 or equivalent document, a list of members of the IRB committee and their qualifications and affiliations prior to authorizing the shipment of study drug supplies to the site. Any amendments to the protocol required IRB approval prior to implementation of any changes made to the study design. No annual IRB re-approvals were required since the study was completed within 1 year. A complete list of documents required prior to initiation of the study is located in the study protocol (Appendix 16.1.1). Information regarding the IRB is presented in Appendix 16.1.3.

5.2   Ethical Conduct of the Study

The study was conducted in accordance with the protocol, GCP, FDA regulations governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki (1996 Version) and all applicable local regulations. The investigator ensured that the study was conducted in accordance with prevailing local laws and customs or complied with the provisions as stated in the FDA guidelines. Responsibilities of the Investigator are specified in the study protocol (Appendix 16.1.1).

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5.3   Subject Information and Consent

The investigator or his/her representative explained the nature of the study to the subject,
and answered all questions regarding this study. Prior to any screening procedures being
performed on the subject, the informed consent statement was reviewed, signed, and
dated by the subject and the person who administered the informed consent. A copy of
the informed consent form was given to the subject and the original was placed in the
subject's medical record. An entry was also made in the subject's dated source
documents to confirm that informed consent was obtained prior to any study-related
procedures and that the subject received a signed copy. Elements of the Informed
Consent are specified in the study protocol (Appendix 16.1.1). A sample copy of the
informed consent is presented in Appendix 16.1.3.

5.4   Subject Confidentiality

All reports and communications relating to subjects in the study identified each subject
only by the subject's initials (first, middle, last) and by the subject's randomization
number. Case report forms (CRF) were used to transmit the information collected in the
performance of this study to Abbott Laboratories and to governmental agencies. Portions
of the subject's medical records pertinent to the study were reviewed by Abbott
Laboratories personnel or their designee and possibly by government personnel to ensure
adequate source documentation, accuracy, and completeness of the CRFs.

The site collected information on the subject per International Conference on
Harmonization (ICH) requirements, including subject name, home address, phone
number, and birthdate. In addition, the name, address, and phone number of another
person who could be contacted in an emergency was also recorded. This information was
treated with strict adherence to professional standards of confidentiality and was filed at
the site.

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Neither the subject, the subject's physician, nor the investigator were informed of the
subject's pharmacogenetic results, if obtained. If performed, the pharmacogenetic results
from individual subjects were kept confidential and were not given to anyone not directly
involved with this research study. The deoxyribonucleic acid (DNA) samples are being
stored by Abbott Laboratories in a secure storage space with adequate measures to protect
confidentiality. The DNA samples are being kept by Abbott Laboratories until destroyed
by Abbott when this research is completed or the required sample retention time has been
satisfied.

6.0   Investigators and Study Administrative Structure

6.1   Investigative Sites

Thirty-four investigators in the United States were recruited to perform the study and
received study drug supplies. Twenty-nine of these investigators randomized at least 1
subject. The study was conducted from 24 April 2000 to 24 February 2001. Complete
names, addresses, and affiliations of the principal investigators are included in
Appendix 16.1.4. The distribution of all enrolled subjects for each investigator is
presented by randomized treatment group in Table 6.1a.

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Table 6.1a   Distribution of Subjects by Investigator and Treatment Group

Investigator	Total Subjects Enrolled	Treatment Group			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
Backonja	3	1	1	0	1
Baumel	15	4	4	4	3
Biton	7	1	2	2	2
Bromberg	13	3	3	4	3
DeBold	12	3	3	3	3
Drucker	6	1	1	2	2
Eisner	6	1	1	2	2
Forde	2	0	0	1	1
Fried	9	2	2	3	2
Gibson	18	5	5	4	4
Gleeson	7	2	2	2	1
Haag	6	1	1	2	2
Hewitt	8	2	2	1	3
Holmlund	5	1	1	1	2
Kafka	7	2	1	2	2
Kipnes	15	4	3	4	4
Kirby	10	3	2	3	2
Kluge	9	2	2	2	3
McGill	8	2	2	2	2
Rowbotham	4	1	1	1	1
Shaibani	17	4	5	4	4
Simmons	6	1	2	2	1
Singer	15	4	4	4	3
Sivakumar	9	2	3	2	2
Steel	8	2	2	2	2
Storey	13	3	4	3	3
Suri	3	1	1	0	1
Vinik	6	2	1	2	1
Weinstein	19	5	4	5	5
Total	266	65	65	69	67

Cross Reference: Table 14.1__1.1

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6.2   Sponsor Information

The sponsor coordinated the activities for initiating this clinical study. The protocol,
CRFs and sample informed consent form were generated by Abbott Laboratories. The
database for this study was created using NOMAD®, a data management system.
Designated statisticians at Abbott Laboratories were responsible for the statistical analysis
of the data. A copy of the signature page for the study summary with the signature of the
Abbott Laboratories' responsible Medical Officer is included in Appendix 16.1.5.

6.3   Contract Research Organization

Abbott Laboratories delegated prestudy (if necessary) and initiation visits, site
monitoring, and post-study site visits to the following Contract Research Organization
(CRO) for the conduct of this clinical study:

> Research Solutions Inc.
> 3200 Chapel Hill Nelson-Highway, Suite 100
> P.O. Box 14561
> Research Triangle Park, NC 27709
> 1-800-807-7462

The sponsor and CRO maintained contact in order to manage adequately the progress of
the study. The CRO coordinated and performed all site visits and prepared trip reports,
using the Abbott Laboratories format, for each visit performed. These reports detailed the
activities conducted at all investigative sites and included all relevant observations. All
trip reports were forwarded to Abbott Laboratories in a timely manner to ensure
appropriate site management, adhering to Abbott Laboratories Standard Operating
Procedures.

6.4   Clinical Supply Management

Clinical supplies were prepared by Abbott Laboratories (Investigational Drug Services,
D-492) for the study and sent to all investigational sites. Abbott Laboratories authorized
the release of clinical supplies once the appropriate essential documents were received
from the respective site and upon approval by Abbott Laboratories Regulatory Affairs.

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All subjects were centrally randomized by site and assigned to a treatment group (using
the randomization supplied by Abbott Laboratories) using an Interactive Voice Response
System (IVRS). The IVRS was contracted from:

> ClinPhone Inc.
> 29 Emmons Drive, C40
> Princeton, NJ 08540

Blinded study medication for each randomized subject (using the randomization supplied
by Abbott Laboratories) was also assigned using the IVRS. Each site kept an accurate
inventory of the clinical supplies, including drug shipping and receiving documents,
dispensing/accountability records, and records for return of clinical supplies to Abbott
Laboratories. Clinical Research Associates (CRAs) from the CRO checked drug
accountability records regularly.

6.5   Central Laboratory

This study utilized 1 central laboratory. All protocol-specified clinical laboratory tests
were performed by the following central laboratory:

> Covance Central Laboratory Services
> 8211 SciCor Drive
> Indianapolis, IN 46214
> (800) 462-8887

The ABT-594 plasma assays were performed under the supervision of Raymond
Wieboldt, Ph.D. of the Drug Analysis Department of Abbott Laboratories, Abbott
Park, IL.

6.6   Administrative Structure

The administrative structure for this study is depicted in Figure 6.6a.

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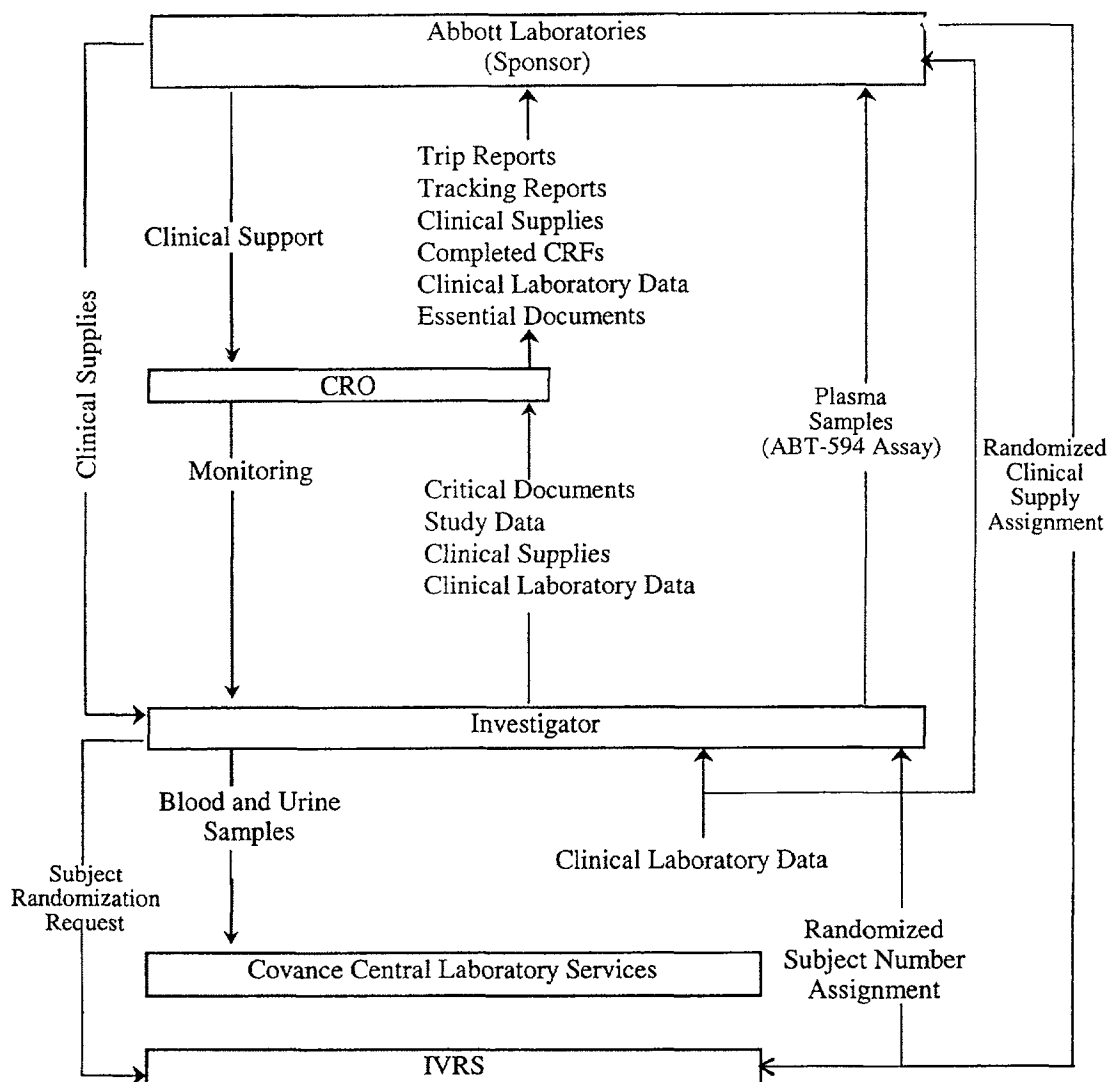
Figure 6.6a   Administrative Structure

7.0   Introduction

7.1   Analgesia Today

Pain is one of the most common reasons people consult a physician, representing an extraordinary societal burden. The cost of chronic pain has been estimated to range in the tens of billions of dollars annually.[1]

Currently there are 4 major groups of therapeutics for pain relief: 1) nonsteroidal anti-inflammatory drugs (NSAIDs/COX-2 inhibitors), 2) opioids, 3) adjuvant analgesics (e.g., tricyclic antidepressants), and 4) centrally acting non-narcotic analgesics (e.g., acetaminophen, tramadol). NSAIDs are most often used to treat mild to moderate pain associated with inflammation, but are ineffective in treating some types of nociceptive and neuropathic pain. Risks associated with NSAIDs include gastrointestinal bleeding and hepatic toxicity. COX-2 inhibitors may improve on this gastrointestinal profile, but other adverse events may become evident. Opioids are used for moderate to severe pain. Clinically significant physical dependence and tolerance to analgesia may occur in subjects receiving opioids regularly. In addition, constipation is a significant side effect. Adjuvant analgesics are commonly used for neuropathic pain. Unlike the other groups, the majority of adjuvant analgesics have a delayed onset of an analgesia because of their mechanism of action and the requirement for dose titration. Therefore, a class of compounds with a broad spectrum clinical activity, efficacy in moderate and severe pain, and without the liabilities of opioids, NSAIDs and other currently available analgesics would represent an important advance in pain relief.

7.2   ABT-594

Interest in the potential analgesic activity of compounds acting at neuronal nicotinic acetylcholine receptors (nAChRs) has been enhanced recently by the discovery that (±)-epibatidine, a potent nAChR agonist, is greater than 100-fold more potent than morphine in rodent models of antinociception.[2] The antinociceptive effects of (±)-epibatidine are blocked by the nAChR antagonist mecamylamine, but not by opioid receptor blockade. Thus, (±)-epibatidine appears to be a potent antinociceptive agent that acts via activation of neuronal nAChRs and not through opioid receptors. Unfortunately, (±)-epibatidine is

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quite potent at all subtypes of the nAChR (neuronal, ganglionic, and neuromuscular junction) and is quite toxic at antinociceptive doses.[3] Because of nAChR diversity, however, it is possible that nAChR ligands with greater receptor subtype selectivity might have therapeutic utility at doses below those associated with side effects.

ABT-594 [(R)-5-(2-azetidinylmethoxy)-2-chloropyridine], is a non-opioid, non-NSAID analgesic. It is a novel neuronal nAChR ligand that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway. It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states.

To date, only systemic treatment with opioids like morphine has been reported to have this broad spectrum of analgesic activity. Like the opioids, ABT-594 can selectively modulate pain transmission by inhibiting substance P release from C-fibers at the level of the dorsal horn, and by activating the brainstem centers that provide descending inhibitory pathways known to gate painful stimuli. In contrast to morphine, repeated treatment with ABT-594 in pre-clinical studies did not produce withdrawal effects at termination of treatment, suggesting an absence of physical dependence liabilities.

In pre-clinical studies, ABT-594 distributes rapidly to the brain following systemic administration and, like morphine, may work at multiple levels in the central and peripheral nervous systems to modulate pain perception. Compounds like ABT-594 that can selectively modulate neuronal nAChR function and possess broad-based antinociceptive activity may provide a novel therapeutic approach to pain management that avoids the liabilities typically associated with opioid analgesics.

Initial clinical trials in humans were conducted using oral solution formulations. Subsequently, a soft elastic capsule (SEC) formulation and, later, a hard gelatin capsule (HGC) formulation were developed and used in clinical trials.

Phase I clinical trials of the oral solution formulations suggested that 150 μg/day would be the maximally tolerated dose. Subsequent experience in Phase I and II trials with the

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solid formulations (SEC and HGC), however, has suggested that higher doses would be tolerated. Preliminary data from Study M99-076 demonstrated that the ABT-594 HGC formulation was generally well tolerated at fixed (untitrated) doses up through 300 µg BID for 14 days. Study M99-120[4] included titrated doses up through 450 µg BID for 5 days. Results from Study M99-120 suggested that a short period of dose escalation at the initiation of therapy improved tolerability. Throughout the Phase I studies of ABT-594, subjects generally tolerated ABT-594 better when dosing followed a meal and after 3-4 days of repeated dosing (the period in which most adverse events occur).

To date, Phase II trials have included efficacy and safety studies of ABT-594 in molar extraction, osteoarthritis and neuropathic pain. Based upon preliminary data from Study M97-772, a study of molar extraction pain, 100 µg ABT-594 (single-dose oral solution) appeared to be a minimally efficacious dose in acute pain.

A study of ABT-594 in osteoarthritis (M98-826)[5] evaluated the ABT-594 SEC formulation at doses of 25, 50 and 75 µg BID for 3 weeks, and a study of ABT-594 in neuropathic pain (M98-833),[6] evaluated the same formulation at doses of 25 and 75 µg BID for 3 weeks. Both studies suggested a trend towards analgesic effect at 75 µg BID. In addition, 75 µg BID was generally well tolerated. The most common adverse events (≥5%) for subjects receiving 75 µg BID ABT-594 in the osteoarthritis and neuropathic pain studies (combined) were nausea (15%), headache (13%), dizziness (7%), insomnia (6%) and vomiting (5%). ABT-594 appeared to be tolerated better after the first week of therapy (an effect not related to premature discontinuations).

Data from the Phase I and II studies completed to date suggest that ABT-594 should be generally well tolerated at doses higher than previously studied in Phase II trials (higher than 75 µg BID). In addition, data from the Phase II trials suggest that, because a trend toward analgesic efficacy was seen at 75 µg BID, a study of higher doses may demonstrate greater analgesic efficacy. The current study, therefore, was performed to test this hypothesis.

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8.0   Study Objective

The objective of this study was to compare the safety and analgesic efficacy of 150 µg,
225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who had painful
distal symmetric diabetic polyneuropathy, had an average of ≥4 points on the diary-based
Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase
(completed on at least 6 of the 7 days), and had ≥4 points on the site-based Pain Rating
Scale (11-Point Likert Scale) at the Baseline Visit.

9.0   Investigational Plan

9.1   Overall Study Design and Plan: Description

This was a Phase II, randomized, double-blind, placebo-controlled, multicenter study to
examine the safety and analgesic efficacy of ABT-594 in subjects who had painful
diabetic polyneuropathy. Approximately 320 subjects were to be assigned randomly in an
equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg BID or placebo
for 49 days on an outpatient basis. Approximately 30 sites were to be recruited in order
to enroll approximately 320 subjects who met entry criteria.

The study was divided into 5 phases: Screening Phase (Day -22 to Day -8), Baseline Pain
Assessment Phase (Day -7 to Day -1), Primer Phase (Day 1 to Day 7), Treatment Phase
(Day 8 to Day 49) and Post-Treatment Phase (Day 50 to Day 59). Day 1 was the first day
of study drug administration. Subjects were allowed a window of ± 3 days for each study
visit. A schematic of the study design is presented in Figure 9.1a.

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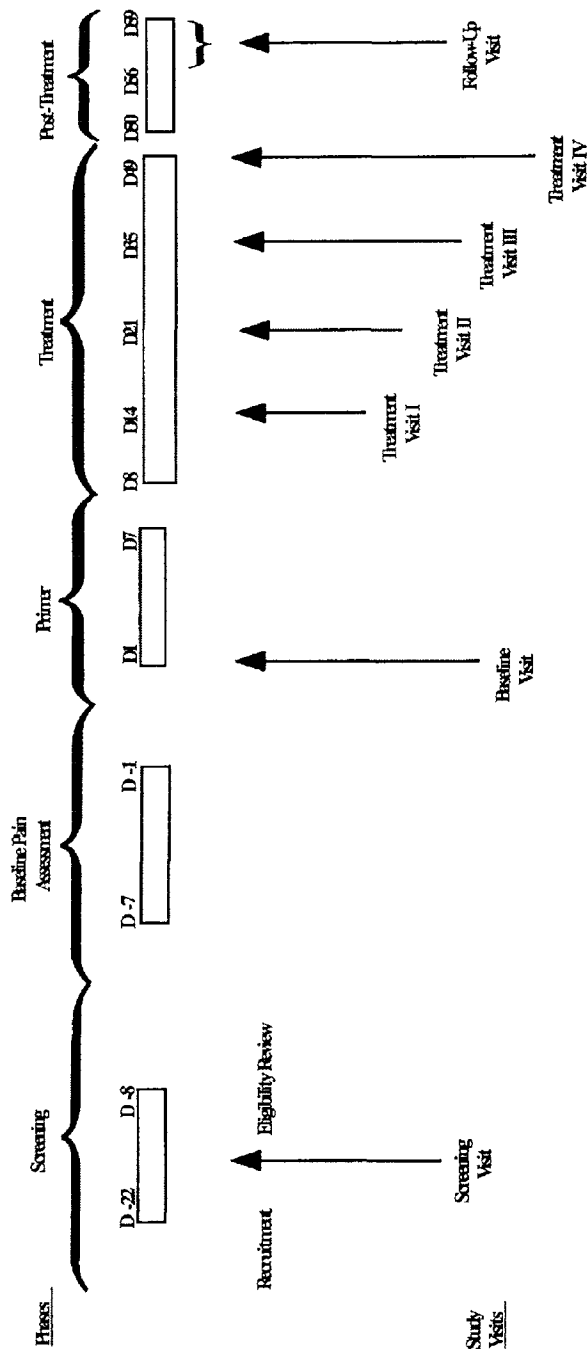
Figure 9.1a   Study Schematic

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Subjects reviewed and signed the informed consent prior to the conduct of any study specific procedures. Subjects were screened for eligibility by medical history, physical examination, vital sign measurements, and clinical laboratory tests. Those subjects taking tricyclic antidepressants, serotonin-specific reuptake inhibitors (SSRIs), antiepileptic drugs, or other analgesics for the treatment of their pain were to have discontinued these drugs at least 7 days prior to the Baseline Pain Assessment Phase. During the Baseline Pain Assessment Phase, at approximately 11 AM each morning, subjects were to complete the diary-based Pain Rating Scale (11-Point Likert Scale) of their diabetic polyneuropathy pain intensity.

On the day after the Baseline Pain Assessment Phase, subjects returned to the site for their Baseline Visit (Day 1). At this visit, diaries were collected and reviewed. In addition, subjects were to complete the site-based Pain Rating Scale (11-Point Likert Scale). Subjects who met all entry criteria, including an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥4 points on the site-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Visit, completed the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute). Subjects underwent an interim medical history, physical examination, vital sign measurements, electrocardiogram (ECG), and clinical laboratory tests.

Subjects who met all entry criteria at the Baseline Visit were randomly assigned in an equal ratio into 1 of 4 treatment groups: ABT-594 150 μg, 225 μg, 300 μg BID, or placebo. Subjects started study drug at the evening dose on Day 1. During the Primer Phase, subjects received a fixed dose escalation of ABT-594 or placebo (Section 9.4.1). The dose was increased every 2 days in 75-μg BID increments until subjects were taking their assigned treatment dose (150 μg, 225 μg, or 300 μg BID). Following the Primer Phase, subjects entered the Treatment Phase (Day 8) and continued their treatment for a total of 49 days.

Throughout the course of the study, subjects were not permitted to take concomitant analgesics, except for limited doses of acetaminophen (3 grams daily maximum or 6 grams maximum during the Baseline Pain Assessment Phase, and 6 grams maximum

per week for each of the 7 weeks of the Primer and Treatment Phases; Section 9.4.7).
Aspirin, 325 mg daily maximum, was permitted if taken for primary prevention of
thromboembolic events and the dose had been stable for ≥ 1 month prior to the Baseline
Visit. Subjects were not allowed to take analgesic medication (including acetaminophen)
within 24 hours of Treatment Visits I, II, III and IV.

Subjects were to complete the diary-based Pain Rating Scale each morning, 3 hours after
taking their morning dose of study drug (approximately 11 AM). They returned to the
site for study procedures on Day 14 (Treatment Visit I), Day 21 (Treatment Visit II) and
Day 35 (Treatment Visit III) and Day 49 (Treatment Visit IV). Procedures during
Treatment Visits I, II, III, and IV included collection of diaries (and issuance of the next
set of diaries at Treatment Visits I, II and III), and the following efficacy and safety
assessments: the site-based Pain Rating Scale, the Neuropathic Pain Scale, the Subject
and Clinician Global Impression of Change (Treatment Visit IV only), the SF-36™
Health Status Survey (Acute; Treatment Visit IV only), physical examination (Treatment
Visit IV only), vital sign measurements, clinical laboratory tests (Treatment Visits I, III
and IV), ECG (Treatment Visit IV only), and ABT-594 plasma assay collection
(Treatment Visits I and IV only). A subset of subjects at selected sites underwent
additional pharmacokinetic sampling at Treatment Visits I and IV.

On the day after Treatment Visit IV, subjects entered the Post-Treatment Phase. Subjects
no longer took study drug or completed pain scales. Subjects could have restarted all
discontinued medications under the guidance of their physician. Subjects returned for
study procedures at the Follow-Up Visit (7 to 10 days after their final study drug dose).
Procedures at the Follow-Up Visit included physical examination, vital sign
measurements, recording of any adverse events since Treatment Visit IV, and re-
examination of any abnormal ECG or clinical laboratory findings present at the previous
evaluation.

For those subjects who participated in clinical studies of ABT-594 and who consented, a
blood sample was collected in order to obtain a sample of genetic material
(deoxyribonucleic acid [DNA]). The DNA sample may be used at a later date to
investigate associations between genetic differences (polymorphisms) and differences in
the way subjects respond to treatment, in terms of efficacy or side-effects or both. If a

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genetic factor in response is identified, it may allow the development of a diagnostic test
to identify those most likely to benefit before actually taking the drug. The sample may
also be used to identify genes involved in painful diabetic polyneuropathy.

Copies of the protocol and amendment, and the CRF are included in Appendices 16.1.1
and 16.1.2, respectively.

9.2   Discussion of Study Design, Including the Choice of Control Groups

The design of this study provided a placebo-control group to assess the analgesic efficacy
of ABT-594. Double-blind, parallel-group designs are generally acknowledged as
standard for unbiased estimates of treatment group differences. Validated pain scales
were employed.

9.3   Selection of Study Population

Approximately 320 subjects were to be randomized and receive study medication in this
study. A subject was randomized in this study provided that he/she met all of the
inclusion criteria outlined in Section 9.3.1 and did not meet any of the exclusion criteria
in Section 9.3.2.

9.3.1   Inclusion Criteria

A subject was to meet all of the following criteria within 22 days before the initial dose of
study drug:

1. Prior to any study specific procedure, voluntary written informed consent was
    obtained from the subject after the purpose and nature of the study were explained.

2. The subject was age 18 or older and in relatively good health with a recent
    stable medical history.

3. The subject's weight was $\leq$ 265 pounds.

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4. A female subject was to be non-lactating and:

    -   of non-childbearing potential (either postmenopausal for at least 1 year or
        surgically sterile, including tubal ligation), <u>or</u>

    -   of childbearing potential using oral or barrier contraceptive methods for at
        least 2 months preceding randomization (and continued the contraceptive
        method through the course of the study).

    All female subjects had a negative β subunit human chorionic gonadotropin
    (β-hCG) at the Baseline Visit. Female subjects of childbearing potential had a
    negative β-hCG at all Treatment Visits.

5. The subject had a diagnosis of diabetes mellitus (Type I or Type II), a diagnosis of
    distal symmetric diabetic polyneuropathy, and good control (in the opinion of the
    investigator) of the subject's serum glucose for at least the last 3 months prior to the
    Screening Visit.

6. The subject had distally and symmetrically decreased or lost vibratory, pin and/or
    light touch sensation on neurological exam and either decreased (or absent) deep
    tendon reflexes or documented abnormal nerve conduction study consistent with a
    distal symmetrical neuropathy.

7. The location and quality of the pain under study were consistent with distal
    symmetric diabetic polyneuropathy in the opinion of the investigator.

8. The subject had distal symmetric diabetic polyneuropathy symptoms (including
    pain) which were stable for at least the last 3 months prior to the Screening Visit
    (defined by the opinion of the investigator).

9. The subject had an average of ≥4 points on the diary-based Pain Rating Scale (11-
    Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at
    least 6 of the 7 days) and ≥4 points on the site-based Pain Rating Scale (11-Point
    Likert Scale) at the Baseline Visit.

9.3.2   Exclusion Criteria

A subject was to be excluded from participation in the study for any of the following
reasons:

1. The subject had a positive test result for drugs of abuse or viral hepatitis at the
    Screening Visit, or had a known history of a positive test result for HIV.

2. The subject had recent (<5 years) history of drug or alcohol abuse or dependence.

3. The subject had an acute or chronic renal or hepatic disorder, psychiatric disease or
    disorder or any uncontrolled medical illness.

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4. The subject had an active malignancy of any type or a history of malignancy
    (excluding basal cell carcinoma that had been treated or other malignancies that had
    been surgically removed and had no evidence of recurrence for a minimum of
    5 years prior to study start).

5. The subject had taken an investigational drug within 1 month prior to
    administration of study treatment or was scheduled to receive an investigational
    drug other than ABT-594 during the course of this study.

6. The subject had a diastolic blood pressure greater than 95 mm Hg and/or a systolic
    blood pressure greater than 170 mm Hg (sitting) at the Screening Visit.

7. The subject had orthostatic hypotension (defined as a decrease in systolic blood
    pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure from supine
    to standing sustained after 1 minute of standing) at the Screening Visit, or a history
    of syncope or pre-syncopal symptoms.

8. The subject had previously participated in a study involving ABT-594, including
    the present study.

9. The subject had clinically significant abnormalities in clinical chemistry,
    hematology, or urinalysis, including aspartate aminotransferase (AST) or alanine
    aminotransferase (ALT) $\geq$ 1.5 times the upper limit of the reference range, a serum
    creatinine >1.5 mg/dL or a hemoglobin A_{1c} >11% (subjects may have had elevated
    serum and urine glucose).

10. The subject had clinically significant electrocardiographic abnormalities.

11. The subject had ongoing treatment with or expected treatment with any medication
    not allowed as described in Section 9.4.7, including at least 7 days prior to the
    Baseline Pain Assessment Phase.

12. The subject had a diagnosis of fibromyalgia, arthritis, bursitis, tendinitis, vascular
    disease or other painful disorders affecting the extremities (other than the
    neuropathy under study) that the subject could not differentiate from the neuropathy
    pain.

13. The subject had sympathetically maintained pain (e.g., Reflex Sympathetic
    Dystrophy, Causalgia), defined by the opinion of the investigator.

14. The subject was unlikely to comply with the study protocol or was unsuitable for
    any other reason, in the opinion of the investigator.

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9.3.3   Removal of Subjects from Therapy or Assessment

A subject could have voluntarily discontinued participation in the study at any time. The investigator may also have decided, for medical reasons or protocol noncompliance, to discontinue prematurely a subject's participation. The investigator was to notify the CRA within 24 hours and document the reason for premature discontinuation on the appropriate CRF.

Subjects whose participation was discontinued prematurely after signing study consent but before study drug administration did not require follow-up observations. Subjects whose participation was discontinued prematurely after study drug administration were to undergo the procedures normally performed at Treatment Visit IV within 7 to 10 days following discontinuation from the study.

If, in the judgment of Abbott Laboratories and possibly in consultation with the investigators, continued exposure to a study drug represented a significant risk to subjects, the study was to be terminated.

9.4   Treatments

9.4.1   Treatments Administered

Subjects were randomly assigned in an equal ratio to 1 of the following 4 treatment groups:

> ABT-594 150 µg BID
> ABT-594 225 µg BID
> ABT-594 300 µg BID
> Placebo for ABT-594 BID

ABT-594 and matching placebo were supplied as Light Gray Opaque No. 1 HGCs.

During the Primer Phase, subjects received a fixed dose escalation of study drug. Study drug was initiated at 75 µg BID. The dose was increased every 2 days in 75-µg BID increments until subjects were taking their assigned treatment dose (150 µg, 225 µg, or 300 µg BID). The ABT-594 dose escalation scheme is presented in Table 9.4a.

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Table 9.4a   ABT-594 Dose Escalation

Treatment Group	Suggested Dosing Time	Days 1-7							Day 8
		1	2	3	4	5	6	7	8
150 µg ABT-594 BID	8 AM		75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
225 µg ABT-594 BID	8 AM		75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
300 µg ABT-594 BID	8 AM		75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg

During the Primer Phase, subjects randomized to placebo received a fixed dose escalation of placebo BID, in a double-blind fashion.

Subjects started study drug at the PM dose on Day 1 (Section 9.4.5). The number and type of HGCs per dose for the Treatment Phase is presented in Table 9.4b.

Table 9.4b   Number and Type of Capsules by Treatment Group

Treatment Group	Number of Capsules Per Dose (Days 8-49)	
	Daily Blister Card (BID doses)	
	75 µg ABT-594 HGC	Placebo ABT-594 HGC
ABT-594 150 µg BID	2	2
ABT-594 225 µg BID	3	1
ABT-594 300 µg BID	4	0
Placebo BID	0	4

9.4.2   Identity of Investigational Product(s)

Information regarding the formulations used in this study is presented in Table 9.4c.

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Table 9.4c   Identity of Investigational Products

Test Preparation	Drug Product Lot #	Drug Substance Lot #	Source
ABT-594 75 μg HGC Formulation A-2	58-293-AR 61-312-AR	52-015-KD-00	Abbott[a]
Placebo HGC No. 1, Light Gray Opaque (Starch)	55-243-AR-01	not applicable	Abbott[a]
[a] PARD Solids Pilot Plant, North Chicago, Illinois.			

The ABT-594 75 μg HGC and placebo HGC were identical in appearance.

A listing of subjects receiving test preparations/investigational products from specific batches is presented in Appendix 16.1.6.

9.4.2.1   Packaging and Labeling

Study drug supplies were blinded and packaged in blister cards in accordance with a randomization schedule supplied by Abbott Laboratories (Department of Clinical Statistics). Daily study medication cards were provided to each subject.

Daily study medication cards were labeled with the Module Number (assigned by Abbott, via IVRS), New Product Research Order (NPRO) number, Abbott address, study number, contents, storage conditions and directions for use.

Space was provided on the label of each carton containing the daily study medication cards to record the subject initials and subject randomization number.

9.4.2.2   Storage and Disposition of Supplies

All clinical supplies were stored in a secure location until dispensed to a subject or until returned to Abbott Laboratories. All blinded study drug supplies were stored at controlled room temperature (68-77° F, see USP).

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9.4.2.3   Drug Accountability

The investigator or designee verified that study drug supplies were received intact and in the correct amounts. This was documented by signing and dating the Clinical Supplies Invoice or similar document. Study drug was dispensed after randomization and assignment of study medication by IVRS (Section 9.4.3) for each subject who met the enrollment criteria. The investigator or designee recorded the subject number, subject initials, and date the study drug was dispensed to the subject on the Abbott Laboratories Drug Accountability Form. The amount of study drug remaining was recorded at Treatment Visits I, II, III and IV for each subject on the M99-114 Final Drug Supply Reconciliation Summary by Investigator Form. An accurate running inventory of study drug was kept and included the NPRO number, Clinical Supplies Invoice number(s), the number of modules dispensed, and the date study drug was dispensed for each subject. An overall accountability of the study drug was performed and verified by the CRA throughout the study and at the site close-out visit. All supplies (unused and empty blister cards) were inventoried, accounted for, and returned to Abbott Laboratories. A copy of the Return of Investigational Drug Supplies for Disposal Form, in accordance with the instructions of the CRA, was also included in the shipment. The investigator agreed not to supply study medication to any persons not enrolled in the study or not named as a subinvestigator on FDA Form 1572.

9.4.3   Method of Assigning Subjects to Treatment Groups

The randomization schedule was computer-generated before the start of the study by Abbott Laboratories Department of Clinical Statistics. All subjects were centrally randomized by investigative site using an IVRS. Before the study was initiated, the telephone number and call-in directions for the IVRS were provided to each site.

Approximately 320 subjects were to be randomized in an equal ratio to receive either ABT-594 150 μg, 225 μg, 300 μg BID or placebo. Subjects were assigned randomization numbers in ascending numerical sequence per investigative site at the Baseline Visit.

The randomization schedule is presented in Appendix 16.1.7.

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9.4.4   Selection of Doses in the Study

ABT-594 doses (150 µg, 225 µg, and 300 µg BID) were selected on the basis of Phase I and Phase II studies, and represent doses below the maximally tolerated dose. Phase II data suggested that ABT-594 doses greater than 75 µg BID may be efficacious in the relief of osteoarthritis and distal symmetrical neuropathy pain.

The selection of BID dosing for ABT-594 was based upon Phase I pharmacokinetic results. ABT-594 doses for the Primer Phase (75 µg, 150 µg, and 225 µg BID) were selected based on Phase I safety and pharmacokinetic data.

9.4.5   Selection and Timing of Dose for Each Subject

During the Primer Phase, subjects started study drug at the evening dose on Day 1 within 1 hour following a meal (e.g., 8 PM). Subjects then took BID doses of ABT-594 (75 µg, 150 µg, 225 µg or placebo during the Primer Phase and ABT-594 150 µg, 225 µg, 300 µg or placebo during the Treatment Phase) within 1 hour following a meal (e.g., at 8 AM and 8 PM).

Study drugs were to be taken with at least 1 cup (8 ounces) of water.

9.4.6   Blinding

Both the investigator and the subject remained blinded to the subject's treatment throughout the course of the study. The study blind may have been broken if, in the opinion of the investigator, it was in the subject's best interest to know the study drug assignment. The sponsor was to be notified before breaking the blind, unless identification of the study drug was required for emergency therapeutic measures. Blind breaking information was to be provided using IVRS. Before the study was initiated, the telephone number and call-in directions for the IVRS were provided to each site. The sponsor was to be notified within 48 hours of the blind being broken. The date and reason for blind breakage were to be recorded on the appropriate CRF.

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9.4.7   Prior and Concomitant Therapy

At the Screening Visit, a history of medications used over the prior 2 weeks was taken.

Concomitant analgesics (prescription or over-the-counter [OTC], except aspirin and acetaminophen as described below), including (but not limited to) serotonin-specific reuptake inhibitors, mixed serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, antiepileptic medications, sodium channel blockers (e.g., mexilitine), opioids, capsaicin, NSAIDs, COX-2 inhibitors, muscle relaxants, transcutaneous electrical nerve stimulation (TENS) and topical analgesics were not allowed. In addition, St. John's Wort was not allowed.

Aspirin, 325 mg daily maximum, was permitted if taken for primary prevention of thromboembolic events and the dose had been stable for ≥ 1 month prior to the Baseline Visit. Acetaminophen, 3 grams daily maximum, or 6 grams maximum during the Baseline Pain Assessment Phase and per week, for each of the 7 weeks of the Primer and Treatment Phases, was permitted. Subjects were not allowed to take analgesic medication (including acetaminophen) within 24 hours of the Baseline and Treatment Visits I, II, III and IV.

If the administration of any concomitant medication was necessary during the course of this study, the medication name, dosage information, frequency and dates of administration was reported on the CRF. Concomitant analgesic medication use (frequency only) was recorded separately on the Concomitant Analgesic Medication Use CRF at the Baseline Visit and at Treatment Visits I, II, III and IV. The concomitant medication use record included the number of separate occasions each subject had used protocol-allowed (limited amounts) acetaminophen and any other analgesic (taken as a protocol violation) since the subject's previous visit.

9.4.8   Treatment Compliance

In order to document compliance with the treatment regimen, subjects were instructed to return all medication cards and cartons (even if empty) to the study coordinator at Treatment Visits I, II, III and IV. Treatment compliance was documented by the investigator or designee on the M99-114 Final Drug Supply Reconciliation Summary by

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Investigator Form and on the appropriate CRF. Overdose information was collected on the appropriate CRF.

9.5   Efficacy, Pharmacokinetic and Safety Variables

9.5.1   Efficacy, Pharmacokinetic and Safety Measurements Assessed and Flow Chart

Study procedures were performed as summarized in Table 9.5a, Study Procedures Flow Chart.

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Table 9.5a   Study Procedures Flow Chart

Study Activity	Screening Phase D-22 and D-8 — Screening Visit	Baseline Pain Assessment Phase D-7 to D-1	Primer Phase D1-D7 — Baseline Visit D1	Primer D2-D7	D8-D49	Treatment Visit D14 (I)	D21 (II)	D35 (III)	D49 (IVa)	Post-Treatment Phase D50-D59 — Follow-Up Visit D56 to D59
Informed Consent	X									
Medical History	X		X^b							
Physical Exam	X^c		X							
Vital Signs	X^d		X^c			X		X	X	X
ECG			X			X		X	X	X^f
Clinical Laboratory Tests^g	X									X^f
Viral Hepatitis Screen	X									
Urine Drug and Alcohol Screen	X									
Pregnancy Test			X			X^h	X^h	X^h	X^h	
Genetic Polymorphism Sample (If Applicable)			X							
ABT-594 Plasma Assay			X			X	X		X	
ABT-594 Pharmacokinetic Profile^i						X			X	
Diary Issued	X		X			X	X	X		
Diary Collected			X			X	X	X	X	
Diary-Based Pain Rating Scale^j		X		X	X					
Site-Based Pain Rating Scale			X			X	X	X	X	
Neuropathic Pain Scale			X			X	X	X	X	
Subject/Clinician Global Impression of Change				X	X	X	X	X	X	
SF-36™			X						X	
Randomize Subject			X							
Dispense Study Drug			X			X^k	X	X		
Analgesic Use Monitoring			X			X	X	X	X	
Adverse Event Monitoring			X			X	X	X	X	X
Concomitant Medication Monitoring			X			X	X	X	X	X
Study Drug Accountability			X			X	X	X	X	

a   Or upon premature discontinuation.
b   Interim history.
c   Included height.
d   Included orthostatic measurements at Screening Visit only.
e   Included oral temperature at Baseline Visit only.
f   Performed only if there were clinically significant abnormalities at the previous evaluation.
g   Chemistry, hematology and urinalysis.
h   Required of all females of child-bearing potential.
i   Study drug was to be taken in front of study staff. Blood samples from selected subjects were taken just prior to dosing (0 hour), and at 1.5, 3, 5, and 8 hours after dosing at selected sites only.
j   To be completed at approximately 11 AM each morning during the Baseline Pain Assessment Phase and approximately 3 hours after the morning dose during the Primer and Treatment Phases.
k   Redispensed study medication for days 15-20 after checking drug accountability.

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9.5.1.1   Efficacy Measurements

Prior to any efficacy measurements, a trained site observer instructed the subject on how to perform and record all pain assessments.

The baseline for all efficacy measurements (except for the diary-based Pain Rating Scale) was the last evaluation performed prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to Day 1 of the study.

Efficacy assessments included the diary- and site-based Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale, the Subject Global Impression of Change, Clinician Global Impression of Change, and SF-36™ Health Status Survey (Acute).

Efficacy measurements were to be performed 3 to 4 hours post dose, when possible.

Pain Rating Scale (11-Point Likert Scale)

Subjects were to assess pain intensity daily by completing the Pain Rating Scale in their diaries. These assessments were to be completed daily at approximately the same time each morning (approximately 11 AM) during the Baseline Pain Assessment Phase and daily at the same time each morning (approximately 3 hours after the morning dose of study medication) during the Primer and Treatment phases. Subjects were to record the time they completed the assessments in their diaries.

Subjects also were to assess pain intensity by completing the Pain Rating Scale at the Investigative Site. These assessments were to be completed at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature discontinuation). The time of assessment was recorded on the appropriate CRF.

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Neuropathic Pain Scale

The Neuropathic Pain Scale was completed by subjects at the Baseline Visit and at
Treatment Visits I, II, III, and IV (or upon premature discontinuation).

Subject Global Impression of Change

The Subject Global Impression of Change of analgesic relief due to study drug was
performed at Treatment Visit IV (or upon premature discontinuation).

Clinician Global Impression of Change

The Clinician Global Impression of Change of a subject's analgesic relief due to study
drug was performed at Treatment Visit IV (or upon premature discontinuation).

SF-36™ Health Status Survey (Acute)

The SF-36™ Health Status Survey (Acute) was completed by each subject at the
Baseline Visit and at Treatment Visit IV (or upon premature discontinuation).

9.5.1.2   Safety Measurements and Procedures

Informed Consent

The investigator or designated representative explained the nature of the study to the
subject and answered all questions regarding this study. Prior to any screening
procedures being performed on the subject, the informed consent statement was
reviewed, signed, and dated by the subject and by the person who administered the
informed consent. A copy of the informed consent form was given to the subject and
the original was placed in the subject's medical record. An entry was also made in
the subject's dated source documents to confirm that informed consent was obtained
prior to any study related procedures and that the subject received a signed copy.

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Medical History

A complete medical history was obtained from each subject during the Screening
Visit. In addition, history of tobacco and alcohol use, and medication (prescription or
OTC) use over the 2 weeks prior to screening was recorded. The medical history was
updated at the Baseline Visit.

Physical Examination

A physical examination, including weight, was performed at the Screening Visit,
Baseline Visit, Treatment Visit IV, and Follow-Up Visit. Height was measured at the
Baseline Visit only. The physical examination performed at the Baseline Visit served
as the baseline physical examination.

Vital Signs

Blood pressure, pulse rate and respiration rate were measured at the Screening Visit,
Baseline Visit, Treatment Visits I, III, and IV, and Follow-Up Visit. Orthostatic
blood pressure and pulse rate were measured at the Screening Visit only. Oral
temperature was taken at the Baseline Visit only. Vital sign measurements at the
Baseline Visit served as the baseline vital sign measurements.

Protocol-specified blood pressure and heart rate measurements (except orthostatic)
were obtained after the subject had been sitting for at least 3 minutes. Orthostatic
measurements were obtained after 3 minutes in the supine position and then after
1 minute in the standing position. Ideally, the subject's blood pressure was to be
measured in the same arm by the same study personnel using the same instrument.

Blood pressure and heart rate measurements were to precede, not follow, scheduled
blood draws. Subjects were kept as calm and undisturbed as possible during blood
pressure and heart rate measurements.

Electrocardiogram (ECG)

A resting 12-lead ECG was obtained at the Baseline Visit and at Treatment Visit IV. An ECG was performed at the Follow-Up Visit only if clinically significant abnormalities were present on the previous evaluation. The ECG performed at the Baseline Visit served as the baseline ECG.

A qualified physician interpreted the ECG. One copy of each 12-lead ECG and physician's report was retrieved by the CRA with the CRF.

Clinical Laboratory Testing

Samples were obtained for the clinical laboratory tests presented in Table 9.5b at the Screening Visit, Baseline Visit, and Treatment Visits I, III, and IV. Laboratory tests were obtained at the Follow-Up Visit only if clinically significant abnormalities were present on the previous evaluation. The laboratory test results obtained at the Baseline Visit served as the baseline results (except for hemoglobin A_{1c}, for which the result obtained at the Screening Visit was used as the baseline result). Blood draws were to be performed after pain assessments or vital sign determinations during a visit.

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Table 9.5b   Clinical Laboratory Tests

Hematology	Blood Chemistry	Urinalysis
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity
Hemoglobin	Creatinine	Ketones
Red Blood Cell (RBC) count	Total Bilirubin	pH
White Blood Cell (WBC) count	Aspartate Aminotransferase/	Bilirubin
Neutrophils	Serum Glutamic-Oxaloacetic Transaminase	Protein
Monocytes	(AST/SGOT)	Blood
Bands	Alanine Aminotransferase/	Glucose
Basophils	Serum Glutamic-Pyruvic Transaminase	Microscopic
Eosinophils	(ALT/SGPT)	evaluation
Lymphocytes	Lactate Dehydrogenase (LDH)	
Hemoglobin A_{1c} (Screening Visit	Alkaline Phosphatase	
and Treatment Visit IV only)	Sodium	
Mean Corpuscular Hemoglobin	Potassium	
(MCH)	Chloride	
Mean Corpuscular Hemoglobin	Calcium	
Concentration (MCHC)	Inorganic Phosphorus	
Mean Corpuscular Volume (MCV)	Uric Acid	
Platelet count (estimate was not	Bicarbonate	
acceptable)	Cholesterol	
Prothrombin Time (PT)	Total Protein	
Partial Thromboplastin Time (PTT)	Glucose	
	Triglycerides	
	Albumin	

A central laboratory was utilized to process and provide results for the clinical laboratory tests.

The investigator reviewed all laboratory test results and assessed the clinical significance for each abnormal result. All laboratory test results that were considered clinically significant by the investigator were followed to satisfactory resolution. A copy of each laboratory report was included with the CRF.

Viral Hepatitis Screen

At the Screening Visit, subjects underwent serological evaluation for viral hepatitis (hepatitis A virus IgM antibody, hepatitis B virus surface antigen, and hepatitis C virus antibody). The hepatitis test panel was performed by the central laboratory.

Urine Drug Screen and Alcohol Screen

Urine specimens, collected at the Screening Visit, were tested for drugs of abuse and alcohol by the central laboratory.

Pregnancy Test

A urine pregnancy test was performed by designated study personnel at the Baseline Visit for all female subjects and at Treatment Visits I, II, III, and IV for female subjects of childbearing potential. A lactating or pregnant female was not eligible for participation in this study.

Adverse Events

An adverse event is defined as any unexpected event(s) such as a disease, syndrome, sign, symptom, and/or laboratory finding associated temporally with the use of drug in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the subject. Subjects were instructed to contact the investigator if an adverse event occurred so that appropriate action could be taken.

All adverse events, whether in response to a query, observed by site personnel, or spontaneously reported by the subject were reported on the appropriate CRF. All adverse events and post-treatment laboratory abnormalities considered clinically significant by the investigator were followed to a satisfactory resolution.

The investigator assessed and recorded any adverse event in detail on the adverse event CRF including the date of onset, description, final diagnosis (if known),

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severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for the event, and action taken. For adverse events to be considered as sporadic, the events must have been of a similar nature and severity.

The investigator used the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator used the following definitions to assess the relationship of the adverse event to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on rechallenge and another etiology is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator opinion of possibly related, probably not related, or not related to study drug was given, an alternate etiology was provided for the adverse event.

Adverse events (including those that met regulatory criteria for a serious adverse event) were monitored continuously from the time of study drug administration to the

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Follow-Up Visit. In addition, adverse events spontaneously reported to the investigator after completion of the Treatment Phase (or after premature discontinuation) were collected up to 30 days after drug discontinuation and reported to Abbott Laboratories. Subjects were instructed to report to the investigator any other adverse events that occurred after the Follow-Up Visit.

Serious adverse events, as well as adverse events that the investigator considered to be related to study design and/or procedures, that occurred after signing the informed consent and prior to the first dose of study drug were also collected.

Any abnormal laboratory value or change in vital signs was not documented as an adverse event unless it was a reason for premature discontinuation from the study, required treatment, or met regulatory criteria for a serious adverse event.

Ongoing medical conditions were considered adverse events if there was an increase in severity or frequency of occurrence. Since measurements of pain intensity were efficacy measurements in this study, an increase in severity or frequency of occurrence of the pain under study was not considered an adverse event for the purposes of this study.

Serious Adverse Events

If an adverse event met any of the following criteria, whether related to study drug or not, the investigator and other professional personnel in attendance was to be notified as soon as possible for the appropriate action. The investigators were to notify Abbott Laboratories by telephone within 24 hours of being made aware of any serious adverse event. In addition, a written confirmation of the occurrence, including any supplementary data, was to be sent within 3 days of the telephone report.

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Death of Subject:	An event which results in the death of a subject.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in fatality if immediate medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an admission to the emergency room or outpatient facility.
Prolongation of Hospitalization:	An event which occurs while the study subject is hospitalized and that prolongs the subject's hospital stay.
Persistent or Significant Disability/Incapacity:	An event which results in a condition that interferes with the activities of daily living of a study subject (e.g., permanent loss of vision).
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that, based on medical judgement, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in the "serious" definition (e.g., allergic bronchospasm requiring intensive treatment in the home or emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

In addition, miscarriage/spontaneous and elective abortions were to be reported to Abbott Laboratories as serious adverse events.

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9.5.2   Appropriateness of Measurements

All efficacy measurements in this study were validated and considered standard for this population. All clinical and laboratory procedures in this study were standard and generally accepted.

9.5.3   Efficacy Variables

9.5.3.1   Primary Variable

The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. The baseline pain score for the diary data was defined as the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1 of the study.

9.5.3.2   Secondary Variables

Change from baseline to final and each scheduled evaluation was calculated for each of the following secondary efficacy variables:

- Diary-based Pain Rating Scale (11-Point Likert Scale), change from baseline to each evaluation only
- Site-based Pain Rating Scale (11-Point Likert Scale)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health][7] physical component summary (PCS), and mental component summary (MCS).[8]

The pain evaluations recorded at the Baseline Visit were used as the baseline score for pain evaluations assessed at the investigative site.

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9.5.4   Drug Concentration Measurements

Blood samples for ABT-594 plasma assay were to be collected from all subjects at Treatment Visits I and IV. One blood sample (approximately 7 mL) was to be collected into a sodium heparin evacuated collection tube at each visit. Blood draws were to be performed after any pain assessments or vital sign determinations during a visit. For subjects who prematurely discontinued, a blood sample was to be taken for ABT-594 assay at the premature discontinuation visit, and the exact time at which the prior dose was taken was to be recorded.

For those subjects participating in the additional pharmacokinetic sampling for pharmacokinetic profile (approximately 30 subjects), blood samples were collected at Treatment Visits I and IV.

After establishing the time of the Treatment Visit, the subject was instructed to take the preceding day's study drug as close as possible to 8 PM. At the office visit, the study medication was taken in the presence of the office staff in order to allow proper and accurate recording of blood collection times relative to dosing. The time of the visit accommodated a target time for the morning dose of 12 hours after the preceding evening's dose. Blood samples were collected as follows: just prior to dosing (0 hour) and at 1.5, 3, 5, and 8 hours after the morning dosing. Subjects received their 8 PM dose as scheduled. Subjects were confined at the site until the 8-hour blood sample was collected.

All blood samples were immediately stored at 4°C or below. The samples were to be separated by centrifugation within 1 hour after collection. The supernatant was to be transferred by polypropylene pipettes into plastic vials clearly marked as "Assay Plasma" and labeled with the study drug number, protocol number, subject number, initials, and date and time of sample collection. This information was also recorded on the appropriate CRF. All labeled plastic vials were placed in a rack to prevent breakage. Plasma samples for determination of ABT-594 were frozen at -5°C or colder within

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1 hour from centrifugation. All specimens were kept frozen at -5°C or colder until
packed in solid carbon dioxide (dry ice) for shipment to Abbott Laboratories.

The time and date of each subject's morning dose on the days of plasma assay blood
draws, the time and date of the meal eaten prior to the morning dose, and the time and
date of the evening dose on the day prior to the plasma assay blood draws were recorded
on the CRF.

Details of the ABT-594 assay methodology will be presented in the Clinical
Pharmacokinetic Report.

9.5.5   Pharmacokinetic Variables

For the subset of subjects who underwent additional pharmacokinetic sampling at
Treatment Visits I and IV, values of AUC, C_{max}, and C_{trough} were to be calculated using
noncompartmental methods.

9.5.6   Blood Samples for Genetic Polymorphism Analysis

Two 10 mL whole blood samples were collected in purple top (EDTA) tubes at the
Baseline Visit and shipped immediately at ambient or refrigerated temperature to
Covance Central Laboratory Services.

If clear differences in response are noted during the clinical development of ABT-594 and
believed to be genetically related, these samples may be analyzed as part of a multicenter,
multistudy project to identify genetic factors involved in the response to ABT-594 or
drugs of this class. The specific response may be related to efficacy or safety, or both.
The results of this potential analysis are not reported with this study summary. The
samples may also be used for development of a diagnostic test for drug response.

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9.6   Data Quality Assurance

Prior to the initiation of this protocol, an investigator's meeting was held with Abbott
personnel, the investigators and their study coordinators, the CRO's project manager and
CRAs. This meeting entailed a detailed discussion of the protocol, CRF completion, and
specimen collection methods. In addition to the investigator's meeting, the study
personnel at each site were trained on the study procedures by a CRA at a study initiation
visit and given a CRF completion workbook for reference. The CRAs monitored each
site approximately every 4 weeks. At each visit, 100% source-document review was
made against the entries on the CRFs and a quality-assurance check was performed to
ensure that the investigator was complying with the protocol and regulations. The
investigator agreed to provide Abbott Laboratories (or designee) access to all source
documents in order to verify CRF entries. In addition, after CRFs were retrieved by the
CRA, a review of the data was conducted by a physician and a clinical review team at
Abbott Laboratories.

The SF-36™ Health Status Survey (Acute) was recorded directly on the CRF and was
considered source data.

All CRFs were to be legible and completed in black ball point ink. All corrections were
initialed and dated by the investigator or designated assistant. The investigator reviewed
the CRFs for completeness and accuracy and signed and dated the set of CRFs where
indicated.

Each CRF was printed on 3-part no carbon required (NCR) paper. The forms consisted
of a white, yellow and pink copy. The white and yellow copies of the completed, verified
CRF were collected by the CRA and the pink copy was retained at the investigative site.

Data captured on the CRF were entered into the database by a double-key entry procedure
at Abbott Laboratories. Discrepancies against the hard-copy CRF were reviewed and
corrected on-line. After completion of the entry process, computer logic checks were run
to check for such items as inconsistent study dates and outlying laboratory values, and

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any necessary corrections were made to the database and documented via addenda or audit trail.

The laboratory results were electronically transferred from the central laboratory to the study database. A final review of all laboratory results was conducted by a physician and clinical review team at Abbott Laboratories.

9.7   Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1   Statistical and Analytical Plans

All statistical tests were 2-tailed and considered statistically significant if the P-value (Type 1 error rate) was less than or equal to 0.05 (when rounded to 3 decimal places).

For all efficacy and safety endpoints, comparisons of primary interest were between each ABT-594 treatment group and the placebo group, along with an assessment of ABT-594 linear dose response. Appropriate secondary comparisons were to be made as considered necessary. No statistical adjustments were made for multiple comparisons.

The baseline for all variables (except for the diary-based Pain Rating Scale) was the last measurement obtained prior to the subject receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to the subject receiving the first dose of blinded study drug on Day 1.

9.7.1.1   Data Sets Analyzed

Efficacy analyses were to be performed for 2 sets of data: intent-to-treat (ITT) subjects and evaluable subjects. Subjects who received at least 1 dose of study drug with at least 1 diary-based baseline and at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert Scale) were included in the ITT

analyses. The evaluable dataset included subjects who received at least 7 days of study drug with at least 1 baseline and at least 1 post Day 7 pain assessment for the diary-based Pain Rating Scale. Safety analyses were performed with all randomized subjects who received at least 1 dose of study drug.

9.7.1.2   Demographic and Other Baseline Characteristics

Baseline comparability among treatment groups for the reasons for premature discontinuation, demographic and baseline pain assessment measurements was assessed. The analyses were performed using 1 or more of the following methods: a 1-way analysis of variance (ANOVA) with treatment group as the main effect for quantitative variables, the Cochran-Mantel-Haenszel (CMH) test for equal row means for ordered categorical variables, and the Fisher's exact test (or its generalization to $r \times c$ tables) for qualitative variables.

9.7.1.3   Efficacy Analyses

For all efficacy variables (except the diary-based Pain Rating Scale), the baseline measurement was the last measurement obtained prior to the subject receiving the first dose of blinded study drug on Day 1. Baseline for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to Day 1 of the study. Change from baseline to each scheduled evaluation was calculated for all efficacy variables (except both Global Impression of Change scores).

Primary Efficacy Analysis

The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug.

Treatment groups differences for the primary efficacy variable were evaluated using a 2-way ANOVA with factors for treatment group, study center, and the treatment

group by study center interaction. If the interaction term was not statistically significant at the 0.10 level, the primary efficacy analysis for the treatment group differences was to be the 2-way ANOVA with factors for treatment group and study center, but without the interaction term. If some study centers had fewer than 1 subject per treatment group in the ITT dataset, data from such centers were to be combined for analysis.

Secondary Efficacy Analysis

Treatment group differences in the mean change from baseline to the final evaluation for the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), including 8 sub-domains and PCS and MCS, and the site-based Pain Rating Scale (11-Point Likert Scale) score were assessed using a 2-way ANOVA as described in the above Primary Efficacy Analysis subsection. The actual scores of each of the Subject and Clinician Global Impression of Change were analyzed using the CMH test for equal row means with study centers as strata. SF-36™ PCS and MCS could have also been analyzed using appropriate regression analysis (with possible factors for demographic variables, treatment and time).

Additionally, treatment group differences in the change from baseline to each scheduled evaluation were assessed, as described for the change from baseline to the final evaluation for the Neuropathic Pain Scale and the site-based Pain Rating Scale (11-Point Likert Scale). For the diary-based Pain Rating Scale (11-Point Likert Scale), change from baseline to each scheduled evaluation was analyzed using the last 7 days prior to each scheduled visit. Subject and Clinician Global Impression of Change was evaluated using CMH methodology on actual scores.

If indicated, exploratory analyses were to be performed on change from baseline pain scores, such as analysis of covariance (ANCOVA), with baseline pain scores as the covariate.

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Dose response for ABT-594 was explored using both a parametric regression model and nonparametric tests, with and without placebo included. If the effect of investigator sites was not significant, then the nonparametric Jonckheere-Terpstra test was to be used instead of Page's test to assess dose response of ABT-594.

Other analyses were to be performed as appropriate.

Missing Data

Two sets of analyses, corresponding to the handling of missing observations, were performed on the efficacy variables. The "last observation carried forward" (LOCF) analyses used the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis had data for each specified evaluation. This technique reduces the bias caused by subjects who prematurely discontinue for lack of efficacy. The "observed cases" (OC) analysis did not estimate the missing evaluation, and a subject who did not have pain evaluation on a scheduled visit was excluded from the OC analysis for that visit.

In the event of data missing from the individual items in the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute), the estimated score of the missing item was calculated, when less than ½ (within the scale of interest) of items are non-missing, as follows:

1. Calculate the ratio of the total score of the scale (the non-missing items) divided by the maximum possible total score for the non-missing items,

2. Multiply the maximum possible scores for the missing item by the ratio obtained in Step 1 above.

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9.7.1.4   Pharmacokinetic Analyses

The maximum observed plasma concentration (C_{max}), the time to C_{max} (T_{max}), and
the trough plasma concentration (C_{trough}) were to be obtained directly from the
plasma concentration-time data. The area under the plasma concentration-time curve
during a dosing interval (AUC) were to be obtained by the trapezoidal rule, using the
Hour 0 concentration value for the Hour 12 value, or by some other appropriate
methodology.

To assess dose proportionality and time invariance, T_{max}, dose-normalized C_{trough}
and log-transformed dose-normalized AUC and C_{max} from the subset of subjects
participating in the additional pharmacokinetic sampling were to be subjected to a
mixed effects model analysis. The model was to include dose, visit (Treatment Visit I
and Treatment Visit IV), and dose by visit interaction as fixed effects. Age, body
weight, nicotine-use status, and other variables that may have accounted for
variability in pharmacokinetics were to be included as covariates. The study center
factor was to be included in the initial model, including a center main effect and,
interaction of center with other factors. The center factor, or at least the interaction
terms involving center, were to be dropped from the model if they explained little of
the variability in the data. If the number of subjects who had only Treatment Visit I
data and not Treatment Visit IV data exceeded 20% of the subjects with additional
pharmacokinetic sampling, then the analyses were also to be performed for each visit
separately. The hypothesis of invariance with dose was to be tested by comparing the
300 µg BID dose versus the 150 µg BID dose. If the hypothesis of dose
proportionality was rejected in a comparison, then the 225 µg BID dose was to be
compared to each of the 150 and 300 µg BID doses. If the visit by dose interaction
was statistically significant, then a comparison was to be made for each visit.

An exploratory analysis was also to be performed on the data set obtained from all
subjects (including those who did not participate in the additional pharmacokinetic
sampling). This analysis was to take into account the appropriate time of sampling

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relative to dosing. The questions of dose proportionality and change from Treatment Visit I to Treatment Visit IV were to be considered in this analysis.

If there was some evidence from the data of this study that ABT-594 was efficacious, then the relationship between ABT-594 plasma concentration and the primary efficacy variable was to be explored, using data from ABT-594 and placebo treatment groups or from ABT-594 treatment groups alone. One exploration was to utilize the data of all subjects. An analysis using only the data of subjects undergoing additional pharmacokinetic sampling was also to be performed. The model was to include effects for efficacy variable baseline value and for visit. The center factor was to be incorporated appropriately. The dependency of the measurements from the same subject was to be accounted for. Other analyses were to be performed as necessary.

9.7.1.5   Safety Analyses

All subjects who received at least 1 dose of study drug were evaluated for safety.

Adverse events were coded using the COSTART V^9 dictionary. Treatment-emergent adverse events (i.e., those which began or worsened in severity after randomized study drug was taken) were tabulated by body system and COSTART term for each treatment group. Treatment group differences were evaluated using Fisher's exact test for the proportion of subjects reporting a particular adverse event. A summary of the severity, relationship to study drug, incidence and prevalence across time of all treatment-emergent adverse events, tabulated by COSTART term and body system, was presented for each treatment group. Analyses by subgroup were performed as appropriate.

Laboratory data were analyzed using a 1-way ANOVA with treatment as the main effect. The primary analyses were the change from baseline to the minimum, maximum, and final values during the study for each laboratory variable.

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Additionally, the number and percentage of subjects with shifts from baseline to the final values using criteria for limits for statistical analysis and normal ranges to define categories (low, normal, high and missing) was summarized.

Laboratory data values were categorized as low, normal, or high based on normal ranges of the central laboratory used in this study. Low or high laboratory values were flagged in the data listings. In addition, laboratory results which satisfied the criteria for limits for statistical analysis were identified.

Mean changes from baseline to the minimum, maximum and final values for vital signs and ECG were analyzed in a similar manner as described for laboratory data above. Vital sign and ECG results which satisfied the criteria for below and above limits were identified.

Concurrent medication use was summarized by treatment group.

Additional safety analyses were to be performed as indicated.

9.7.2   Determination of Sample Size

The study was designed to enroll approximately 320 subjects (approximately 80 subjects in each treatment group). This sample size should have allowed for the detection of a 0.46 effect size in the average diary-based Pain Rating Scale score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two-tailed Type I error) level with at least 80% power. This calculation was based on results obtained from Study M98-833[6] of ABT-594 and published data using Gabapentin for subjects with painful diabetic polyneuropathy[10] and assuming a 39% and 25% improvement from baseline for ABT-594 and placebo, respectively.

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9.8   Changes in the Conduct of the Study or Planned Analyses

9.8.1   Protocol Changes

Significant changes in the developmental strategy of ABT-594 resulted in the study being prematurely discontinued by the sponsor. Therefore, although the protocol specified that approximately 320 subjects (80 per treatment group) were to be enrolled, enrollment was stopped at 266 subjects.

The final clinical protocol incorporated Amendment Number 1. All subjects were enrolled under the final protocol (Table 14.1__2). Full details of the clinical protocol and its amendment are presented in Appendix 16.1.1. Important changes included in the amendment are summarized below:

Amendment 1 (29 February 2000)

- Modified the inclusion criteria such that subjects were required to have good control (in the opinion of the investigator) of their serum glucose for at least the last 3 months prior to the Screening Visit.
- Added that subjects with a hemoglobin A_{1c} >11% were to be excluded.
- Added hemoglobin A_{1c} at the Screening Visit and Treatment Visit IV and deleted the hemoglobin A_{1c} at the Baseline Visit.
- Added mixed serotonin and norepinephrine reuptake inhibitors and St. John's Wort to the list of excluded medications.
- Added that the Screening hemoglobin A_{1c} result served as the baseline result.

9.8.2   Statistical Changes

Although not specified in the protocol, efficacy analyses were also performed on a dataset that included subjects who did not prematurely discontinue from the study (study completers).

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The change from baseline of the average diary-based Pain Rating score from each
subject's diary to the corresponding average of each of the consecutive 7-day intervals
after the first dose of study drug was summarized using both LOCF and OC techniques.

The percentage of subjects having a positive response to study drug, defined as a 50% or
greater improvement from baseline to final, was analyzed for the following variables:
diary- and site-based average Pain Rating Scale scores and Neuropathic Pain Scale Total
Scores. Comparisons between treatment groups were performed using the CMH test,
with investigator as the stratification variable.

10.0   Study Subjects

10.1   Disposition of Subjects

The location of premature discontinuation data is presented below.

Assessment	Statistical Analyses Table	Individual Subject Listing Appendix
Number and Percentage of Subjects Prematurely Discontinued	14.1__3.1	16.2__1.1
Listing of Subject Numbers by Reason for Premature Discontinuation	14.1__3.2	16.2__1.1
Subjects Who Prematurely Discontinued and Any Adverse Events for Which Study Drug was Prematurely Discontinued	14.1__3.3	16.2__1.1 16.2__7.1.1
Number of Subjects Who Prematurely Discontinued by Days of Exposure to Study Drug	14.1__3.4	16.2__1.1 16.2__5.1.1 16.2__5.1.2
Number and Percentage of Subjects that Prematurely Discontinued for Each Investigator	14.1__3.5	16.2__1.1
Previous and Concurrent Medications (Subjects Who Prematurely Discontinued)	none	16.2__1.1 16.2__1.2

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Two hundred sixty-six (266) subjects were enrolled by 29 investigators. Of the 266
subjects, 65 were randomized to receive placebo, 65 were randomized to receive
ABT-594 150 µg BID, 69 were randomized to receive ABT-594 225 µg BID, and 67
were randomized to receive ABT-594 300 µg BID. All 266 subjects who received study
drug are included in the analyses of all treated subjects. Additionally, 3 subjects were
randomized although they failed to meet admission criteria. These subjects did not
receive study drug and are not included in the database.

The proportion of subjects prematurely discontinuing from the study was statistically
significantly different among the treatment groups, with 14 (22%) subjects in the placebo
treatment group, 25 (38%) subjects in the ABT-594 150 µg BID treatment group, 39
(57%) subjects in the ABT-594 225 µg BID treatment group, and 50 (75%) subjects in
the ABT-594 300 µg BID treatment group. A statistically significant difference was also
observed among the treatment groups for the proportion of subjects prematurely
discontinuing from the study due to 1 or more adverse event, which was the most
frequently reported reason for premature discontinuation (9% placebo, 28% ABT-594
150 µg BID, 46% ABT-594 225 µg BID, and 66% ABT-594 300 µg BID). Subject
disposition is presented in Table 10.1a.

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Table 10.1a   Disposition of Subjects

	Treatment Group n (%)			
		ABT-594		
	Placebo	150 µg BID	225 µg BID	300 µg BID
Number of Subjects Planned	80	80	80	80
All Treated Subjects	65	65	69	67
Completed Study	51 (78%)	40 (62%)	30 (43%)	17 (25%)
Prematurely Discontinued[a]	14 (22%)	25 (38%)	39 (57%)	50 (75%)
Adverse Event	6 (9%)	18 (28%)	32 (46%)	44 (66%)
Lack of Efficacy	6 (9%)	6 (9%)	2 (3%)	5 (7%)
Withdrew Consent	2 (3%)	3 (5%)	6 (9%)	5 (7%)
Subject Noncompliant	1 (2%)	3 (5%)	4 (6%)	2 (3%)
Lost to Follow-up	0	0	1 (1%)	2 (3%)
Other[b]	1 (2%)	1 (2%)	3 (4%)	2 (3%)

a   Subjects may have reported more than 1 reason for premature discontinuation, but were counted only once in the total.
b   Description of reason designated as "other": subject stopped taking study drug (2 subjects), initiation of exclusionary medication, medical records noting subject is an alcoholic, refusal to return for follow-up, out of town for 6 weeks, and randomization error (1 subject each).

Cross Reference: Tables 14.1__3.1 and 14.1__3.3 and Appendix 16.2__1.1

A graphic disposition of all subjects is presented in Figure 10.1a.

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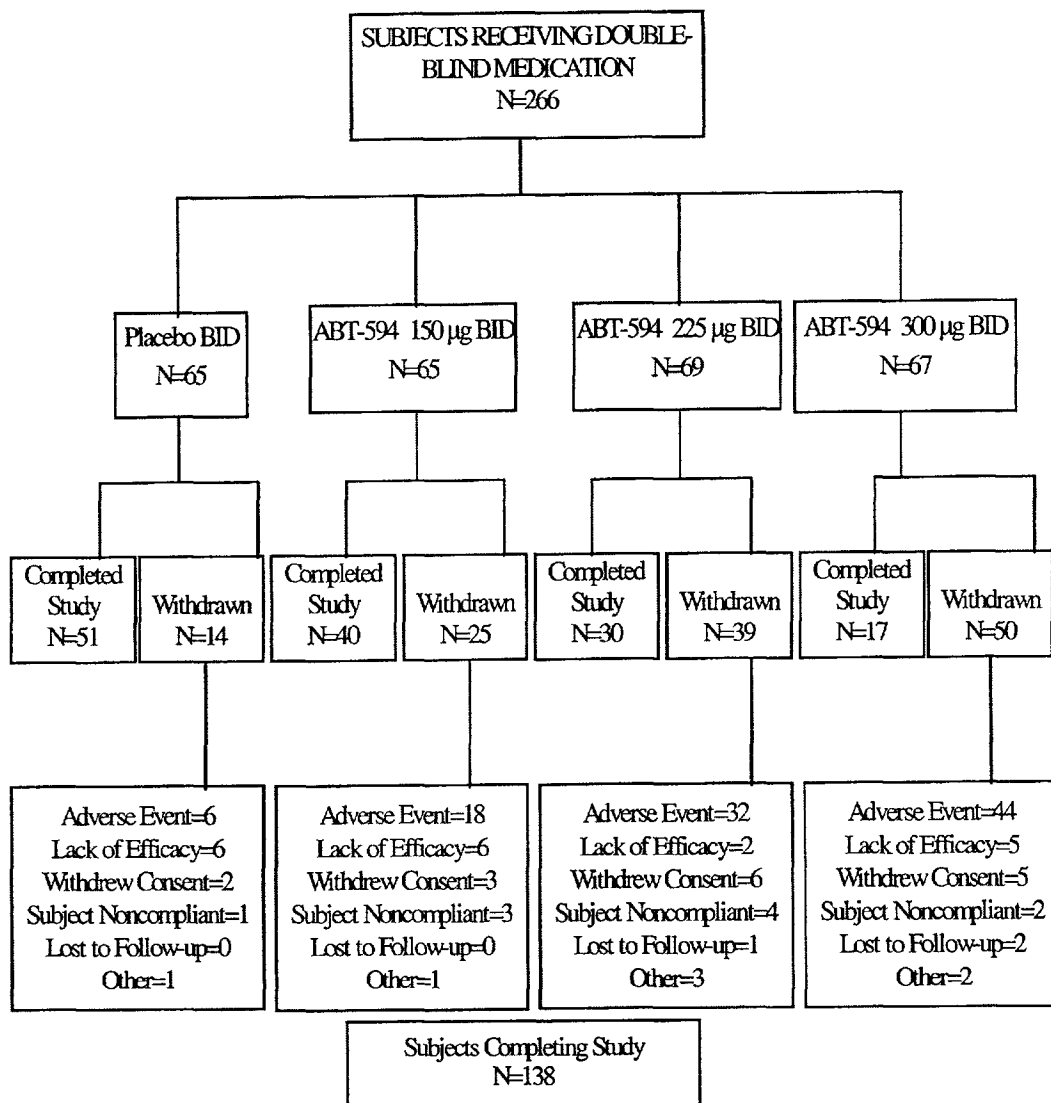
Figure 10.1a   Disposition of Subjects
Note: Subjects may have reported more than 1 reason for premature discontinuation, but were counted only once in the total.

10.2 Protocol Deviations

The location of protocol deviation data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Admission Criteria	none	16.2__2.1
Blind Broken	none	16.2__1.3
Urine Drug Screen	none	16.2__2.2
Hepatitis Screen	none	16.2__2.3
Pregnancy Test Results	none	16.2__2.4
Other Medications and Supplements	none	16.2__7.3

In reviewing the data for all subjects, deviations from the protocol were identified. Clinically significant inclusion/exclusion criteria deviations included the following: failure to perform a pregnancy test at the Baseline Visit (19 subjects), current or expected use of an exclusionary medication (10 subjects), failure to have an average of ≥ 4 points on the diary-based Pain Rating Scale during the Baseline Pain Assessment Phase and ≥ 4 points on the site-based Pain Rating Scale at the Baseline Visit (6 subjects), acute or chronic renal or hepatic disorder, psychiatric disease or disorder or any uncontrolled medical illness (2 subjects), and failure to have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy (2 subjects). These and other minor deviations were not considered important enough to affect the outcome of the study.

One hundred twenty (15 placebo, 30 ABT-594 150 μg, 34 ABT-594 225 μg, and 41 ABT-594 300 μg BID) of the 266 subjects (45%) did not have at least 1 blood sample collected for pharmacokinetic analysis. The remaining 146 subjects (55%) had at least 1 blood sample collected. At the time of this report, the pharmacokinetic analyses were incomplete. Results from the pharmacokinetic analyses will be presented in a separate report.

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Study drug dosing errors were noted for 3 subjects. At the Baseline Visit, Primer Phase modules 17011 and 17001 were incorrectly dispensed to Subjects 4136 (placebo) and 4134 (ABT-594 150 µg BID), respectively. These subjects took incorrect study drug on Study Days 1 through 7. The subjects were also dispensed Treatment Phase modules at the same visit and these modules were dispensed correctly. Therefore, subjects 4136 and 4134 were each taking their correct randomized dose beginning on Study Day 8. One subject (4099) randomized to ABT-594 225 µg BID actually received ABT-594 300 µg BID (module 30157) on Study Days 21 through 37 (Appendix 16.2__5.1.1). In all efficacy and safety analyses, data for Subject 4099 were included in the ABT-594 225 µg BID treatment group.

11.0   Efficacy and Pharmacokinetic Evaluation

11.1   Data Sets Analyzed

The 266 randomized subjects who received at least 1 dose of study drug comprise the "all treated subjects" dataset and are included in the safety analyses. The primary efficacy dataset was the ITT dataset, which included all randomized subjects who took at least 1 dose of study drug and had at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert Scale). Of the 266 all treated subjects, 251 were included in the ITT dataset (Tables 14.2__1.1 and 14.2__1.2).

In addition, efficacy analyses based on "evaluable" and "completers" data were performed. The 217 subjects who received at least 7 days of study drug and who had at least 1 pre-dose pain assessment and at least 1 post-Day 7 pain assessment for the diary-based Pain Rating Scale comprised the "evaluable" efficacy dataset (Tables 14.2__8.1 and 14.2__8.2). The 138 subjects who did not prematurely discontinue from the study for any reason were included in the completers data set. Efficacy ITT, evaluable, and completer exclusions are identified in the data listings.

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The treatment groups were similar with respect to the number and percentage of subjects contributed by each investigator in the ITT and evaluable datasets (Table 14.1__1.2).

A summary of subject accountability is presented in Table 11.1a.

Table 11.1a   Disposition of Subjects by Dataset

| | Treatment Group | | | |
| | | ABT-594 | | |
	Placebo	150 µg BID	225 µg BID	300 µg BID
Number of Subjects Planned	80	80	80	80
Number of Subjects Randomized	65	65	69	67
Subjects Included in the All Treated Subjects Dataset	65	65	69	67
Subjects Included in the Intent-to-Treat Dataset	62	61	66	62
Subjects Included in the Efficacy Evaluable Dataset	61	53	54	49
Subjects Included in the Completers Dataset	51	40	30	17

Cross Reference: Table 14.1__1.2 and Appendices 16.2__3.1, 16.2__3.2, and 16.2__3.3

PART 3

11.2   Demographic and Other Baseline Characteristics

All demographic and other baseline characteristic results are for all treated subjects, unless otherwise specified. The location of demographic and other baseline characteristic data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Demographics	14.1__4.1	16.2__4.1
Medical History	14.1__5.1 14.1__5.2	16.2__4.2
Nicotine Consumption	14.1__4.1	16.2__4.3
Baseline Pain Assessments	14.1__6	16.2__6.2.1 16.2__6.2.2 16.2__6.3.1 16.2__6.3.2 16.2__6.4.1 16.2__6.4.2 16.2__6.4.3

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11.2.1   Demographics

No statistically significant differences were observed among treatment groups for sex, race, age, height, or weight. The average age was 61.9 years (range = 20 - 86 years). Eighty-nine percent of the subjects were white. Subject demographic characteristics are presented in Table 11.2a.

Table 11.2a   Demographic Characteristics (All Treated Subjects)

| Demographic Characteristic | Treatment Group n (%) | | | | p-value[a] |
| | Placebo (N=65) | ABT-594 | | | |
		150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)	
Sex					0.870
Female	27 (42%)	31 (48%)	33 (48%)	30 (45%)	
Male	38 (58%)	34 (52%)	36 (52%)	37 (55%)	
Race[b]					0.751
White	57 (88%)	58 (89%)	64 (93%)	59 (88%)	
Black	7 (11%)	6 (9%)	3 (4%)	8 (12%)	
Asian	0	1 (2%)	1 (1%)	0	
Native American	0	0	1 (1%)	0	
Other	1 (2%)	0	0	0	
Age (years)					0.110
Mean (SD)	60.2 (11.43)	60.8 (10.78)	61.8 (11.80)	64.7 (11.10)	
Min-Max	20 - 80	36 - 85	24 - 84	31 - 86	
Height (inches)[c]	(N=65)	(N=65)	(N=69)	(N=66)	0.300
Mean (SD)	68.4 (4.47)	67.5 (3.93)	67.1 (4.27)	67.3 (3.73)	
Min-Max	60 - 77	59 - 75	59 - 79	60 - 75	
Weight (pounds)[c]					0.758
Mean (SD)	205.3 (36.44)	200.0 (40.03)	199.2 (34.57)	203.1 (34.94)	
Min-Max	127.9 - 275.0	113.0 - 276.0	112.0 - 258.0	134.5 - 277.8	

[a]   p-values are from extension of Fisher's exact test comparing treatment groups (sex, race), or a 1-way ANOVA model comparing treatment groups (age, height, and weight).
[b]   Non-white races were combined for calculation of p-value. American Indian/Alaska Native was represented as Native American.
[c]   At baseline.

Cross Reference: Table 14.1__4.1 and Appendix 16.2__4.1

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11.2.2   Other Baseline Characteristics

There were no statistically significant differences among treatment groups in the ITT
analysis with respect to all pain assessment variables (including diary- and site-based Pain
Rating Scale scores and Neuropathic Pain Scale Total Score) and other baseline
characteristics including nicotine use. The baseline characteristics for the ITT dataset are
presented in Table 11.2b.

Pain assessment scales are presented in Appendix 16.1.13.

Table 11.2b   Other Baseline Characteristics (Intent-to-Treat Dataset)

Baseline Characteristic	Treatment Group				p-value[a]
	Placebo	ABT-594			
		150 μg BID	225 μg BID	300 μg BID	
Diary-Based Pain Scale[b]	(N=62)	(N=64)	(N=67)	(N=66)	0.847
Baseline Mean (SD)	6.5 (1.43)	6.6 (1.69)	6.7 (1.51)	6.7 (1.74)	
Site-Based Pain Scale[b]	(N=64)	(N=64)	(N=69)	(N=66)	0.608
Baseline Mean (SD)	6.5 (1.67)	6.7 (1.98)	6.7 (1.57)	6.9 (1.91)	
Neuropathic Pain Scale Total Score[c]	(N=64)	(N=65)	(N=69)	(N=64)	0.910
Baseline Mean (SD)	56.5 (17.47)	55.1 (17.47)	56.3 (15.18)	57.3 (19.81)	
Nicotine Use[d]	(N=65)	(N=65)	(N=69)	(N=67)	0.098
Former User	29 (45%)	24 (37%)	18 (26%)	25 (37%)	
Non-User	32 (49%)	31 (48%)	40 (58%)	38 (57%)	
Current User	4 (6%)	10 (15%)	11 (16%)	4 (6%)	

[a] p-values are from extension of Fisher's exact test comparing treatment groups (nicotine use) or 1-way
      ANOVA model comparing treatment groups (pain scores).
[b] Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.
[c] Neuropathic pain scale (sum of 10 items): 11-Point Likert Scale (0-10), 0 = none, 10 = most.
[d] Former users and non-users were combined for calculation of p-value.

Cross Reference: Tables 14.1__4.1, 14.1__6 and Appendices 16.2__4.3, 16.2__6.2.1, 16.2__6.2.2,
                 16.2__6.3.1, 16.2__6.4.1, 16.2__6.4.2, and 16.2__6.4.3

A medical history was obtained for each subject who entered the study. Among currently
symptomatic subjects, sporadic statistically significant differences were observed between
each of the ABT-594 150 μg BID and 300 μg BID treatment groups and the placebo

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treatment group for the proportions of subjects who had a specific condition/diagnosis
(Table 14.1__5.1). Among currently asymptomatic subjects, no apparent differences
were observed between treatment groups for the proportion of subjects with a specific
condition/diagnosis (Table 14.1__5.2).

11.2.3 Concurrent Medication Use

The proportion of subjects using a concomitant medication during the study was similar
among treatment groups. The number and proportion of subjects who took concomitant
medications during the study and listing of subject numbers by therapeutic classifications
are presented in Tables 14.1__7.1 and 14.1__7.2, respectively. Individual subject data
listings for subjects who took previous and concomitant medications are presented in
Appendix 16.2__7.3.

During the Baseline Pain Assessment Phase, no statistically significant difference was
observed among treatment groups for the proportion of subjects who used protocol-
allowed concomitant analgesic medication (Table 14.2__7.1).

11.3 Measurements of Treatment Compliance

The location of compliance and drug concentration data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Study Drug Administration	14.1__8	16.2__5.1.1
		16.2__5.1.2
Plasma Assay	none	16.2__5.3.1
		16.2__5.3.2

11.4 Efficacy Evaluations and Tabulations of Individual Subject Data

Each efficacy analysis compared the placebo treatment group versus each of the other
ABT-594 treatment groups. Efficacy scale ranges are presented in Appendix 16.1.13.

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11.4.1   Efficacy Analyses

The location of efficacy data is presented below.

Assessment	Statistical Analyses Tables[a]	Individual Subject Listing Appendix
Diary-Based Pain Rating Scale	14.2__2.1.1.1 14.2__2.1.1.2 14.2__2.1.2 14.2__2.1.3 14.2__2.1.4 14.2__2.2 14.2__2.3 14.2__2.4.1.1 14.2__2.4.1.2 14.2__2.4.2 14.2__2.4.3 14.2__2.4.4	16.2__6.2.1
Site-Based Pain Rating Scale	14.2__3.1.1 14.2__3.1.2 14.2__3.1.3 14.2__3.2 14.2__3.3 14.2__3.4	16.2__6.2.2
Neuropathic Pain Scale	14.2__4.1.1 14.2__4.1.2 14.2__4.1.3 14.2__4.1.4 14.2__4.2 14.2__4.3 14.2__4.4	16.2__6.3.1 16.2__6.3.2
Global Impression of Change	14.2__5.1 14.2__5.2 14.2__5.3 14.2__5.4	16.2__6.5
SF-36™ Health Status Survey	14.2__6	16.2__6.4.1 16.2__6.4.2 16.2__6.4.3
Concomitant Analgesic Medication Use	14.2__7.1 14.2__7.2 14.2__7.3	16.2__7.4

[a]   Statistical analyses tables for the ITT dataset.

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Analyses were performed on the ITT, evaluable, and study completers datasets using both
the LOCF and OC methods; the ITT dataset was the protocol-defined primary dataset.
Efficacy results are presented only for the ITT dataset. Efficacy results for the evaluable
and study completers dataset were generally similar to those for the ITT dataset
(Tables 14.2__8.1 through 14.2__13 and 14.2__14.1.1.1 through 14.2__18, respectively).
Furthermore, results from analyses that used the OC method were generally similar to
those that used the LOCF method, and differences are noted between the 2 methods.

11.4.1.1   Primary Efficacy Variable

Diary-Based Pain Rating Scale Scores at Final Evaluation

The mean improvement from baseline to final for the average diary-based Pain Rating
Scale scores was statistically significantly greater for each of the ABT-594 treatment
groups compared to placebo. A summary of the mean change from baseline to final
for the average diary-based Pain Rating Scale scores is presented in Table 11.4a.

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Table 11.4a   Summary of the Analysis of Mean Change From Baseline[a] to Final[b] for the Average Diary-Based Pain Rating Scale[c] Scores Using LOCF Method (Intent-to-Treat Dataset)

| | Treatment Group | | | |
| | Placebo (N=58) | ABT-594 | | |
		150 μg BID (N=56)	225 μg BID (N=58)	300 μg BID (N=53)
Baseline Visit Model-Based Mean (SE)[d]	6.5 (0.21)	6.6 (0.22)	6.7 (0.21)	6.7 (0.22)
Change to Final Model-Based Mean (SE)[d]	-1.1 (0.29)	-1.9 (0.30)*	-1.9 (0.29)*	-2.0 (0.30)*

SE = standard error.
a   Average of the last 7 pain scores prior to Day 1 of the study.
b   Average of the values from the last 7 days on study drug.
c   Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.
d   Least square means from 2-way ANOVA without interaction.
*   Statistically significant difference versus placebo treatment group ($p \leq 0.05$).

Cross Reference: Tables 14.2__2.1.1.1 and 14.2__2.1.1.2 and Appendix 16.2__6.2.1

A statistically significant linear dose response was observed for mean change from baseline to final for the average diary-based Pain Rating Scale scores, in the model that included the placebo treatment group (Table 14.2__2.3).

11.4.1.2   Secondary Efficacy Variables

Change From Baseline to Final

The mean improvement from baseline to final for the average site-based Pain Rating Scale scores was statistically significantly greater in each of the ABT-594 treatment groups compared to placebo.

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There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. However, sporadic statistically significant differences were observed between placebo and 1 of the ABT-594 treatment groups for the mean change from baseline to final in the following items from the Neuropathic Pain Scale: intense, dull, and deep pain (Table 14.2__4.1.2).

In the analysis of the mean change from baseline to final in the SF-36™ Health Status Survey, a statistically significant difference was observed between the ABT-594 225 µg BID and placebo treatment groups in the physical component summary. Subjects in the ABT-594 225 µg BID treatment group showed a greater improvement from baseline compared to subjects in the placebo treatment group. Additionally, a statistically significant difference was observed between the ABT-594 300 µg BID and placebo treatment groups in the mental component summary. Subjects in the placebo treatment group showed an improvement from baseline, while subjects in the ABT-594 300 µg BID treatment group showed a deterioration from baseline. There were no other statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the SF-36™ Health Status Survey subscales.

A summary of the mean change from baseline to final for secondary efficacy variables is presented in Table 11.4b.

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Table 11.4b   Change from Baseline to Final for Secondary Efficacy Variables[a] Using LOCF Method (Intent-to-Treat Dataset)

Variable	Placebo	Treatment Group		
		ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Average Site-Based Pain Rating Scale[b] Scores	(N=57)	(N=47)	(N=40)	(N=29)
Baseline Visit				
Model-Based Mean (SE)[c]	6.4 (0.25)	6.7 (0.27)	6.4 (0.30)	6.7 (0.34)
Change to Final				
Model-Based Mean (SE)[c]	-1.1 (0.36)	-2.7 (0.39)*	-2.1 (0.43)*	-2.8 (0.49)*
Neuropathic Pain Scale[d] Total Score	(N=57)	(N=48)	(N=40)	(N=29)
Baseline Visit				
Model-Based Mean (SE)[c]	54.3 (2.32)	54.6 (2.55)	53.5 (2.82)	56.3 (3.16)
Change to Final				
Model-Based Mean (SE)[c]	-11.4 (3.04)	-16.1 (3.34)	-15.8 (3.69)	-19.7 (4.14)
SF-36™ Health Status Survey Physical Component[e]	(N=58)	(N=54)	(N=59)	(N=54)
Baseline Visit				
Model-Based Mean (SE)[c]	35.0 (1.29)	32.7 (1.36)	32.7 (1.28)	34.3 (1.31)
Change to Final				
Model-Based Mean (SE)[c]	0.6 (0.97)	3.2 (1.02)	3.3 (0.96)*	0.7 (0.98)
SF-36™ Health Status Survey Mental Component[e]	(N=58)	(N=54)	(N=59)	(N=54)
Baseline Visit				
Model-Based Mean (SE)[c]	47.9 (1.50)	50.5 (1.59)	50.6 (1.49)	49.6 (1.52)
Change to Final				
Model-Based Mean (SE)[c]	1.7 (1.29)	-0.9 (1.35)	-1.3 (1.27)	-1.9 (1.30)*

NOTE: Due to the number of subjects who dropped out or failed to complete certain efficacy assessments, the number of subjects included in each of the secondary efficacy analyses was smaller than that of the primary analyses.

[a] Pain assessment scales are presented in Appendix 16.1.13.
[b] Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.
[c] Values represent model-based means (SE) which are least square means from 2-way ANOVA without interaction.
[d] Neuropathic pain scale (sum of 10 items): 11-Point Likert Scale (0-10), 0 = none, 10 = most for each of the 10 items.
[e] Results based on transformed scores as calculated using SF-36™ health survey manual and interpretation guide.
* Statistically significant difference versus placebo treatment group (p≤0.05).

Cross Reference: Tables 14.2__3.1.1, 14.2__4.1.1, and 14.2__6 and Appendices 16.2__6.2.2, 16.2__6.3.1, 16.2__6.4.1, and 16.2__6.4.2

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Global Impression of Change

No statistically significant differences were observed between the placebo and each of the ABT-594 treatment groups in the mean overall change from baseline in the subject and clinician global impression of change. However, each of the ABT-594 treatment groups was numerically better than placebo. A summary of the mean change from baseline to final for subject and clinician global impression of change is presented in Table 11.4c.

Table 11.4c   Change from Baseline to Final for Subject and Clinician Global Impression of Change[a] Using LOCF Method (Intent-to-Treat Dataset)

| | Treatment Group | | | |
| | | ABT-594 | | |
Variable	Placebo	150 µg BID	225 µg BID	300 µg BID
Subject Global Impression of Change[b]	(N=61)	(N=59)	(N=61)	(N=59)
Univariate Mean Change (SE)[c]	0.8 (0.18)	0.8 (0.21)	1.3 (0.21)	1.1 (0.19)
Clinician Global Impression of Change[b]	(N=61)	(N=59)	(N=60)	(N=59)
Univariate Mean Change (SE)[c]	0.7 (0.17)	0.8 (0.21)	1.2 (0.18)	1.1 (0.18)

[a] Pain assessment scales are presented in Appendix 16.1.13.
[b] Overall change defined as follows: 3 = much improved, 2 = moderately improved, 1 = minimally improved, 0 = no change, -1 = minimally worse, -2 = moderately worse, -3 = much worse.
[c] Values represent univariate means (SE) for the Cochran-Mantel-Haenszel test.
Cross Reference: Table 14.2__5.3 and Appendix 16.2__6.5

In the distribution analyses of subject and clinician global impression of change (much, moderately, or minimally improved, no change, or much, moderately, or minimally worse) statistically significant differences from placebo were observed for the ABT-594 225 µg BID treatment group (Table 14.2__5.1). When responses were further categorized as improved (including much, moderate, or minimal), no change,

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or worsened (including much, moderate, or minimal), there was a statistically
significant difference between the ABT-594 225 μg BID and placebo treatment
groups for clinician global impression of change. Based on the clinician's
assessment, a greater proportion of subjects in the ABT-594 225 μg BID treatment
group were improved (63%) compared to subjects in the placebo treatment group
(42%; Table 14.2__5.2).

Dose Response

A statistically significant linear dose response was observed for mean change from
baseline to final for the average site-based Pain Rating Scale scores, in the model that
included the placebo treatment group (Table 14.2__3.3). No statistically significant
linear dose response was observed for mean change from baseline to final for the
Neuropathic Pain Scale Total Score, regardless of whether the model included or
excluded the placebo treatment group (Table 14.2__4.3).

Change From Baseline to Each Week - Diary-Based Pain Rating Scale

Improvements from baseline were seen in diary-based Pain Rating Scale scores at
each week for all treatment groups. In the LOCF analyses, the ABT-594 150 μg BID
treatment group had statistically significantly greater mean improvements from
baseline to Weeks 5, 6, and 7 for the average diary-based Pain Rating Scale scores
when compared to placebo. No statistically significant differences were observed
between the ABT-594 225 μg BID and placebo treatment groups at any time point.
The mean improvements from baseline to Weeks 3, 4, 5, and 7 for the average diary-
based Pain Rating Scale scores were statistically significantly greater in the ABT-594
300 μg BID treatment group compared to placebo. Results of OC analyses were
generally similar to those of LOCF analyses, with a more consistent treatment effect
observed in the OC analyses. A summary of the mean change from baseline to each
week for the average diary-based Pain Rating Scale scores is presented in
Table 11.4d.

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Table 11.4d   Summary of the Analysis of Mean Change From Baseline[a] to Each Week for the Average Diary-Based Pain Rating Scale[b] Scores Using LOCF and OC Methods (Intent-to-Treat Dataset)

	Treatment Group							
			ABT-594					
	Placebo		150 µg BID		225 µg BID		300 µg BID	
	LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC
Visit	(N=58)	(N=[c])	(N=56)	(N=[c])	(N=58)	(N=[c])	(N=53)	(N=[c])
Baseline Mean[d]	6.5	6.5[e]	6.6	6.6	6.7	6.7	6.7	6.7
Week 1[d]	-0.6[f]	-0.6	-0.8	-0.8	-0.8	-0.8	-0.7	-0.7
Week 2[d]	-1.0[f]	-1.0	-1.1	-1.1	-1.2	-1.3	-1.4	-1.8*
Week 3[d]	-1.0	-0.9	-1.2	-1.4	-1.5	-2.0*	-1.7*	-2.4*
Week 4[d]	-1.1	-1.1	-1.6	-1.9*	-1.5	-2.3*	-1.9*	-2.4*
Week 5[d]	-1.0	-1.0	-1.8*	-2.3*	-1.7	-2.5*	-1.9*	-2.9*
Week 6[d]	-1.1	-1.1	-1.9*	-2.4*	-1.7	-2.6*	-1.8	-2.8*
Week 7[d]	-1.1	-1.0	-1.9*	-2.4*	-1.8	-2.6*	-1.9*	-3.1*

LOCF = last observation carried forward; OC = observed cases.
Note: All values represent model-based means.
a   Average of the last 7 pain scores prior to Day 1 of the study.
b   Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.
c   No's for observed cases analyses:

		ABT-594		
	Placebo	150 µg BID	225 µg BID	300 µg BID
Week 1	57	56	58	53
Week 2	56	49	44	38
Week 3	56	47	37	27
Week 4	52	44	34	23
Week 5	50	39	33	20
Week 6	50	39	30	17
Week 7	49	38	29	17

d   Least square means from 2-way ANOVA without interaction.
e   N = 58 at baseline.
f   N = 57 at Weeks 1 and 2.
*   Statistically significant difference versus placebo treatment group (p≤0.05).

Cross Reference: Tables 14.2__2.1.3 and 14.2__2.4.3 and Appendix 16.2__6.2.1

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Change From Baseline to Each Visit - Diary-Based Pain Rating Scale

Each treatment group showed improvement from baseline to the 7-day average prior to each visit in diary-based Pain Rating Scale scores. The mean changes from baseline to Treatment Visits III and IV for the average diary-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 150 μg BID and 225 μg BID treatment groups compared to placebo. Furthermore, the mean changes from baseline to Treatment Visits II, III, and IV for the average diary-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 300 μg BID treatment group compared to placebo (Table 14.2__2.1.2). Results of OC analyses were generally similar to those of LOCF analyses (Table 14.2__2.4.2).

Change From Baseline to Each Visit - Site-Based Pain Rating Scale

Each treatment group showed improvement from baseline to each visit in site-based Pain Rating Scale scores. The mean changes from baseline to Treatment Visits II, III, and IV for the average site-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 150 μg BID treatment group compared to placebo. The mean change from baseline to Treatment Visit IV for the average site-based Pain Rating Scale score was statistically significantly greater in the ABT-594 225 μg BID treatment group compared to placebo. The mean changes from baseline to each Treatment Visit for the average site-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 300 μg BID treatment group compared to placebo (Table 14.2__3.1.2). Results of OC analyses were generally similar to those of LOCF analyses (Table 14.2__3.4).

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11.4.1.3   Other Efficacy Variables

Proportion of Responders

The percentage of subjects having a positive response to study drug, defined as a 50% or greater improvement from baseline to the final evaluation, was analyzed for the following efficacy variables: average diary- and site-based Pain Rating Scale scores and Neuropathic Pain Scale Total Score. Comparisons between treatment groups were performed using the CMH test, with investigator as the stratification variable.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either the diary- or site-based average Pain Rating Scale scores at the final evaluation compared to subjects in the placebo treatment group. A summary of the proportion of subjects with a positive response to study drug as measured by average diary- and site-based Pain Rating Scale scores is presented in Table 11.4e.

Table 11.4e   **Proportion of Subjects Responding[a] to Treatment as Measured by Diary- and Site-Based Pain Rating Scale Scores[b] Using LOCF Method (Intent-to-Treat Dataset)**

| | Treatment Group | | | |
| | | ABT-594 | | |
Variable	Placebo	150 µg BID	225 µg BID	300 µg BID
Average Diary-Based Pain Rating Scale[c] Scores	(N=58) 12%	(N=56) 27%*	(N=58) 26%	(N=53) 26%*
Average Site-Based Pain Rating Scale[c] Scores	(N=57) 14%	(N=47) 40%*	(N=40) 35%*	(N=29) 48%*
[a] Defined as a 50% or greater improvement from baseline to the final evaluation.				
[b] Pain assessment scales are presented in Appendix 16.1.13.				
[c] Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.				
* Statistically significant difference versus placebo treatment group ($p \leq 0.05$).				

Cross Reference: Tables 14.2__2.1.4 and 14.2__3.1.3 and Appendices 16.2__6.2.1 and 16.2__6.2.2

Concomitant Analgesic Medication Use

No statistically significant differences were observed among the treatment groups for the proportion of subjects using any analgesic medication or within 24 hours of analgesic medication at each visit during the Treatment Phase and over the entire Treatment Phase (Tables 14.2__7.1 and 14.2__7.2). There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the number of times analgesic medication was used (Table 14.2__7.3).

11.4.2   Statistical and Analytical Issues

11.4.2.1   Adjustments for Covariates

Adjustments for covariates, including sex, race, age, and weight, were not performed in the efficacy analyses.

11.4.2.2   Handling of Dropouts or Missing Data

Two sets of efficacy analyses, corresponding to the handling of missing data, were performed. The LOCF analyses used the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis had a value for each specified evaluation. This technique was intended to reduce bias caused by subjects who prematurely discontinued due to lack of efficacy. The OC method did not estimate missing evaluations and a subject who did not have a pain evaluation on a scheduled visit was excluded from the OC analysis for that visit. Results obtained with the OC method were generally consistent with those obtained with the LOCF method.

11.4.2.3   Interim Analyses and Data Monitoring

No interim analyses were performed.

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11.4.2.4   Multicenter Studies

This was a multicenter study. The treatment-by-center interaction was not statistically
significant at an α=0.10 in the analysis of change from baseline to the final evaluation
for the diary-based Pain Rating Scale scores (Table 14.2__2.2), indicating
homogeneity of treatment effects across centers for the primary endpoint. Therefore,
the treatment-by-center interaction term was not used in the primary or secondary
analyses. Additionally, since the treatment-by-center interaction term was not used in
the primary analysis, data from study centers with less than 1 subject per treatment
group in the ITT dataset, were not combined for the analyses.

11.4.2.5   Multiple Comparisons/Multiplicity

No statistical adjustments were made for multiple comparisons.

11.4.2.6   Use of an "Efficacy Subset" of Subjects

Subjects who received less than 7 days of study drug or who had no baseline or post
Day 7 pain assessment for the diary-based Pain Rating Scale were identified prior to
breaking the blind and were excluded from the evaluable dataset. Results for ITT and
evaluable datasets were similar.

11.4.2.7   Active-Control Studies Intended to Show Equivalence

The study was not designed to assess equivalence to an active control.

11.4.2.8   Examination of Subgroups

Subgroup analyses for potentially influential factors were not performed.

11.4.3   Tabulation of Individual Response Data

There were no tabulations of individual response to study drug except as provided in the data listings (Appendix 16.2).

11.4.4   Drug Dose, Drug Concentration, and Relationship to Response

Blood samples for ABT-594 plasma assay were to be collected for all subjects at Treatment Visits I and IV. For those subjects participating in the pharmacokinetic sampling for pharmacokinetic profile (approximately 30 subjects), additional blood samples were collected at Treatment Visits I and IV. Plasma concentrations of ABT-594 are listed for each subject in Appendix 16.2__5.3.1.

A complete discussion of the pharmacokinetic variables analyzed will be presented in a separate Clinical Pharmacokinetic Report.

11.4.5   Drug-Drug and Drug-Disease Interactions

Analyses which examined drug-drug and drug-disease interactions were not performed.

11.4.6   By-Subject Displays

There were no by-subject displays of individual response to study drug except as provided in the data listings (Appendix 16.2).

11.4.7 Efficacy Conclusions

ABT-594 at 150 µg, 225 µg, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. Statistically significant linear dose responses were observed in the model that included the placebo treatment group for mean change from baseline to final for the average diary- and site-based Pain Rating Scale scores.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to the subjects in the placebo treatment group.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline to final in SF-36™ Health Status Survey, a statistically significant improvement was observed for the ABT-594 225 µg BID treatment group in the physical component summary compared to the placebo treatment group. However, statistically significant worsening was observed for the ABT-594 300 µg BID treatment group in the mental component summary compared to the placebo treatment group.

11.5 Pharmacokinetic Variables

Complete pharmacokinetic results will be presented in a separate Clinical Pharmacokinetic Report.

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12.0 Safety Evaluation

All 266 randomized subjects who were treated with study drug (65 placebo, 65 ABT-594 150 µg, 69 ABT-594 225 µg, and 67 ABT-594 300 µg BID) were evaluated for safety. Adverse events, clinical laboratory data, vital signs (including weight), and 12-lead ECG data were used to evaluate safety.

12.1 Extent of Exposure

The mean duration of treatment was statistically significantly different among treatment groups. The placebo treatment group received study drug for a mean 44.3 days, as compared to 35.9, 28.6, and 22.7 days for the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups, respectively. A summary of the extent of exposure to study drug is presented in Table 12.1a.

Table 12.1a   Extent of Exposure

| Duration of Treatment (Days) | Treatment Group n (%) | | | |
| | Placebo (N=65) | ABT-594 | | |
		150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
<7	1 (2%)	8 (12%)	14 (20%)	12 (18%)
7 - 13	2 (3%)	5 (8%)	14 (20%)	19 (28%)
14 - 20	4 (6%)	4 (6%)	4 (6%)	6 (9%)
21 - 27	5 (8%)	6 (9%)	3 (4%)	8 (12%)
28 - 34	0	2 (3%)	0	3 (4%)
35 - 41	1 (2%)	0	4 (6%)	2 (3%)
42 - 48	3 (5%)	5 (8%)	3 (4%)	1 (1%)
≥49	49 (75%)	35 (54%)	27 (39%)	16 (24%)
Mean (SD)*	44.3 (13.5)	35.9 (19.1)	28.6 (20.5)	22.7 (18.0)

Note: Percentages may not sum to 100 due to rounding.
SD = standard deviation.
*   Statistically significant difference among treatment groups ($p \leq 0.05$).
Cross Reference: Table 14.1__8 and Appendix 16.2__5.1.1

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12.2 Adverse Events

The location of adverse event data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Adverse Events		16.2__7.1.1
All Treatment-Emergent	14.3.1__1.1	
by Severity	14.3.1__1.2.1	
	14.3.1__1.2.2	
by Relationship to Study Drug	14.3.1__1.3.1	
	14.3.1__1.3.2	
Incidence Across Time	14.3.1__2.1	
Prevalence Across Time	14.3.1__2.2	
Identification of Subjects	14.3.1__3.1	
Medical Terms and Descriptions Associated with Each COSTART Term	14.3.1__3.2	

12.2.1 Brief Summary of Adverse Events

Among all treated subjects, 66% of subjects who received placebo and 83%, 90%, and
91% of subjects who received ABT-594 150 µg, 225 µg, and 300 µg BID, respectively,
reported treatment-emergent adverse events. The overall incidence of adverse events was
statistically significantly higher for each of the ABT-594 treatment groups than for the
placebo treatment group. The most frequently reported ($\geq$10% of subjects in any
ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness,
vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had
statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and
46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%,
22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared
to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A
statistically significantly greater proportion of subjects in the ABT-594 225 µg BID and

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300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%,
respectively) compared to subjects in the placebo treatment group (2%). Subjects in the
placebo treatment group had a statistically significantly greater incidence of treatment-
emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment
group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg
BID) died 58 days after completion of the Treatment Phase. The subject died due to
suicide, which the investigator considered to be unrelated to study drug. In addition to
the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and
4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these
subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID)
reported serious adverse events associated with the cardiovascular system during the
study. Each subject had multiple risk factors for cardiovascular disease. One hundred
subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg
BID) prematurely discontinued study drug due to 1 or more adverse events. The most
frequently reported (≥10% of subjects in any ABT-594 treatment group) adverse events
leading to discontinuation among ABT-594 subjects were nausea, vomiting, dizziness,
abnormal dreams, and headache.

12.2.2   Display of Adverse Events

A summary of the treatment-emergent adverse events occurring in ≥10% of subjects in
any ABT-594 treatment group is presented by the investigator's assessment of
relationship to study drug in Table 12.2a.

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Table 12.2a   Summary of Most Frequently Reported[a] Treatment-Emergent Adverse Events By Relationship to Study Drug

	Treatment Group n (%)																							
COSTART Term	Placebo (N=65)						150 µg BID (N=65)						225 µg BID (N=69)						300 µg BID (N=67)					
	Relationship[b]				Total		Relationship[b]				Total		Relationship[b]				Total		Relationship[b]				Total	
	NR	PN	PO	PR	n	%	NR	PN	PO	PR	n	%	NR	PN	PO	PR	n	%	NR	PN	PO	PR	n	%
Any Event					43	66%					54	83%*					62	90%*					61	91%*
Nausea	0	0	2	5	7	11%	0	1	5	16	22	34%*	1	0	5	24	30	43%*	1	0	3	27	31	46%*
Dizziness	1	1	0	1	3	5%	0	1	2	8	11	17%*	0	3	3	18	24	35%*	0	0	3	17	20	30%*
Vomiting	0	0	1	1	2	3%	0	0	1	9	10	15%*	1	0	3	13	17	25%*	1	1	1	11	14	21%*
Abnormal Dreams	0	0	0	0	0		0	0	2	12	14	22%*	0	0	1	14	15	22%*	0	0	2	10	12	18%*
Headache	2	2	3	1	8	12%	3	3	3	4	13	20%	2	2	0	6	10	14%	1	0	1	11	13	19%
Asthenia	0	0	0	1	1	2%	0	0	3	1	4	6%	0	0	3	8	11	16%*	0	1	2	11	14	21%*
Diarrhea	0	0	0	2	2	3%	1	2	2	2	7	11%	2	0	2	4	8	12%	1	1	0	2	4	6%
Dyspepsia	0	0	2	0	2	3%	0	0	3	2	5	8%	0	0	0	8	8	12%	0	0	1	4	5	7%
Insomnia	0	1	2	0	3	5%	0	0	1	0	1	2%	1	1	2	5	9	13%	0	0	2	5	7	10%

NR = not related; PN = probably not related; PO = possibly related; PR = probably related.

a Adverse events occurring in ≥10% of subjects in any ABT-594 treatment group.

b As assessed by the investigator.

* Statistically significant difference versus the placebo treatment group (p≤0.05).

Cross Reference: Tables 14.3.1_1.1, 14.3.1_1.3.1 and 14.3.1_1.3.2 and Appendix 16.2_7.1.1

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Most adverse events in all treatment groups were mild or moderate in severity and were
considered by the investigator to be possibly or probably related to study drug
(Tables 14.3.1__1.2.1, 14.3.1__1.2.2, 14.3.1__1.3.1, and 14.3.1__1.3.2).

12.2.3   Analysis of Adverse Events

The overall incidence of treatment-emergent adverse events was statistically significantly
higher for subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups
(83%, 90%, and 91%, respectively) than for subjects in the placebo treatment group
(66%). Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had
statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and
46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%,
22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared
to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A
statistically significantly greater proportion of subjects in the ABT-594 225 µg BID and
300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%,
respectively) compared to subjects in the placebo treatment group (2%). Subjects in the
placebo treatment group had a statistically significantly greater incidence of treatment-
emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment
group (3%). No other statistically significant treatment differences were observed for any
specific treatment-emergent adverse event (Table 14.3.1__1.1).

Five percent (3/65) of placebo-treated subjects, 11% (7/65) of ABT-594 150 µg-treated
subjects, 12% (8/69) of ABT-594 225 µg-treated subjects, and 12% (8/67) of ABT-594
300 µg BID-treated subjects experienced at least 1 severe adverse event, most of which
were considered probably related to study drug by the investigator. The remaining
adverse events were mild or moderate in severity. A summary of the severity of
treatment-emergent adverse events grouped by body system and COSTART term is
presented in Tables 14.3.1__1.2.1 and 14.3.1__1.2.2.

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12.2.4   Listing of Adverse Events by Subject

The location of adverse event data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Treatment-Emergent Adverse Events Grouped by Body System, COSTART Term, Medical Term, and Description With Subject Number Identification (All Treated Subjects)	14.3.1__3.1	16.2__7.1.1
Adverse Event Medical Terms and Descriptions	14.3.1__3.2	

12.3   Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

The location of deaths, other serious adverse events, and other significant adverse event data is presented below.

Assessment	Statistical Analyses Tables	Narrative Section	Individual Subject Listing Appendix
Deaths	14.3.2__1.1	14.3.3	16.2__7.2
Serious Adverse Events	14.3.2__1.2	14.3.3	16.2__7.1.2
Treatment-Emergent Adverse Events for Which Study Drug was Prematurely Discontinued	14.3.2__2	14.3.3	16.2__7.1.1
Number and Percentage of Subjects With Treatment-Emergent Adverse Events for Which Study Drug was Prematurely Discontinued Grouped by Body System and COSTART Term	14.3.2__3		16.2__7.1.1

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12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1 Deaths

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug.

A listing of subjects who died during the course of the study is presented in Appendix 16.2__7.2.

12.3.1.2 Other Serious Adverse Events

In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) reported a serious adverse event during the study (Table 14.3.2__1.2). One of these subjects reported an event (palpitation reported in an ABT-594 300 µg BID-treated subject) considered probably related to study drug. The event was a single occurrence and resolved within 90 minutes. Another 1 of the 13 subjects (ABT-594 300 µg BID) reported a serious adverse event (COSTART term: accidental injury [described as "status post fall down stairs"]) with onset >30 days after the last dose of study drug.

Eight subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each of these subjects had multiple risk factors for cardiovascular disease. Subjects reporting serious adverse events (including death) during the study are presented in Table 12.3a.

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Table 12.3a   Subjects Reporting Serious Adverse Events During the Study

Treatment Group	Investigator/ Subject	Age (yrs)/ Sex	Day of Onset[a]	Day of Resolution[a]	COSTART Term - Reason Serious[b]	Relationship to Study Drug
Placebo	DeBold/4053	52/F	52 (2)	53 (3)	Gastroenteritis - HO	Not related
			52 (2)	53 (3)	Dehydration - HO	Not related
			52 (2)	53 (3)	Ketosis - HO	Not related
	Singer/4401	53/M	34	42 (1)	Angina Pectoris[c] - HO	Not related
			49 (9)	unknown	Atrial Fibrillation - HO	Not related
	Weinstein/4027	65/F	9 (1)	12 (4)	Cerebrovascular Accident[c] - HO	Probably not
ABT-594 150 μg BID	Baumel/4149	71/M	65 (15)	66 (16)	Angina Pectoris - HO	Not related
			65 (15)	66 (16)	Myocardial Infarct - HO	Not related
	Fried/4083	66/F	15 (1)	17 (3)[d]	Syncope[c] - HO	Not related
			15 (1)	22 (3)[d]	Atrial Fibrillation[c] - HO	Not related
	Kipnes/4070	48/F	10	12	Pain[c] - HO	Not related
	Singer/4412	57/M	36	50	Peripheral Vascular Disorder - HO	Not related
	Storey/4100[e]	56/F	79 (58)[f]	79 (58)	Suicide Attempt - DEA	Not related
ABT-594 225 μg BID	Kluge/4133	66/M	6	9	Gastrointestinal Disorder[c] - HO	Not related
	Shaibani/4451	60/F	18	18	Dyspnea[c] - HO	Probably not
			18	20 (2)	Angina Pectoris[c] - HO	Probably not
ABT-594 300 μg BID	Drucker/4002	70/M	4	4	Palpitation[c] - HO	Probably
	Holmlund/4193[e]	55/M	40 (32)[f]	64 (56)	Accidental Injury[g] - HO	Not related
	Holmlund/4197	62/F	5	6 (1)	Angina Pectoris[c] - HO	Not related
	Weinstein/4031	80/M	43 (7)	80 (44)[d]	Cellulitis[c] - HO	Not related

M = male, F = female.
[a]   Number in parentheses represents the number of days after the last dose of study drug.
[b]   HO=hospitalization; DEA=death.
[c]   Adverse event leading to premature discontinuation.
[d]   Adverse event was ongoing as of this day.
[e]   Subject prematurely discontinued due to another adverse event.
[f]   Adverse event onset >30 days after the last dose of study drug.
[g]   Described as status post fall down stairs.

Cross Reference: Table 14.3.2__1.2 and Appendices 16.2.__7.1.1 and 16.2__7.1.2

A listing of all subjects who experienced serious adverse events during the study is presented by treatment group and subject number in Table 14.3.2__1.2.

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12.3.1.3   Other Significant Adverse Events

One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported ($\geq$10% of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

A summary of adverse events leading to premature discontinuation of study drug is presented by treatment group in Table 12.3b.

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Table 12.3b   Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug (All Treated Subjects)

| | Treatment Group n (%) | | | |
| | | ABT-594 | | |
COSTART Term	Placebo (N=65)	150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
Any Event[a]	6 (9%)	18 (28%)*	32 (46%)*	44 (66%)*
Nausea	1 (2%)	8 (12%)*	15 (22%)*	20 (30%)*
Dizziness	0	4 (6%)	11 (16%)*	13 (19%)*
Vomiting	0	4 (6%)	10 (14%)*	12 (18%)*
Abnormal Dreams	0	3 (5%)	6 (9%)*	7 (10%)*
Headache	0	1 (2%)	3 (4%)	8 (12%)*
Insomnia	0	1 (2%)	5 (7%)	4 (6%)
Asthenia	0	0	3 (4%)	6 (9%)*
Dyspepsia	0	2 (3%)	4 (6%)	3 (4%)
Diarrhea	0	0	4 (6%)	2 (3%)
Pain	0	1 (2%)	1 (1%)	4 (6%)
Sweating	0	1 (2%)	2 (3%)	2 (3%)
Chills	0	0	2 (3%)	2 (3%)
Flatulence	1 (2%)	0	1 (1%)	2 (3%)
Hypertension	0	0	2 (3%)	2 (3%)
Nervousness	0	0	3 (4%)	1 (1%)
Abdominal Pain	0	0	1 (1%)	2 (3%)
Angina Pectoris	1 (2%)	0	1 (1%)	1 (1%)
Chest Pain	0	0	1 (1%)	2 (3%)
Dyspnea	0	0	1 (1%)	2 (3%)
Palpitation	0	0	1 (1%)	2 (3%)
Taste Perversion	0	2 (3%)	0	1 (1%)
Abnormal Gait	0	0	2 (3%)	0
Accidental Injury	1 (2%)	0	0	1 (1%)
Amblyopia	0	1 (2%)	1 (1%)	0
Anorexia	0	0	1 (1%)	1 (1%)
Confusion	0	0	1 (1%)	1 (1%)
Hallucinations	0	0	2 (3%)	0
Malaise	0	0	1 (1%)	1 (1%)
Paresthesia	0	0	1 (1%)	1 (1%)
Tachycardia	0	0	1 (1%)	1 (1%)
Thinking Abnormal	0	0	0	2 (3%)
Abdomen Enlarged	0	0	0	1 (1%)
Abnormal Vision	0	0	0	1 (1%)
Alopecia	0	0	1 (1%)	0
Anxiety	0	0	1 (1%)	0
Arthralgia	0	0	1 (1%)	0
Ataxia	0	0	1 (1%)	0
Atrial Fibrillation	0	1 (2%)	0	0
Back Pain	0	0	0	1 (1%)

[a] Subjects may have reported more than 1 adverse event leading to premature discontinuation, but were counted only once in the total.

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

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Table 12.3b   Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug (All Treated Subjects; continued)

COSTART Term	Treatment Group n (%)			
	Placebo (N=65)	ABT-594		
		150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
Cellulitis	0	0	0	1 (1%)
Cerebrovascular Accident	1 (2%)	0	0	0
Depersonalization	1 (2%)	0	0	0
Depression	0	0	0	1 (1%)
Dry Mouth	0	0	0	1 (1%)
Emotional Lability	0	0	1 (1%)	0
Eructation	0	0	0	1 (1%)
Eye Disorder	0	0	1 (1%)	0
Flu Syndrome	0	0	0	1 (1%)
Gastroenteritis	1 (2%)	0	0	0
Gastrointestinal Disorder	0	0	1 (1%)	0
Glossitis	0	1 (2%)	0	0
Hyperglycemia	0	0	0	1 (1%)
Infection	1 (2%)	0	0	0
Leg Cramps	0	0	0	1 (1%)
Myalgia	0	0	1 (1%)	0
Rash	0	0	0	1 (1%)
Rectal Hemorrhage	0	0	0	1 (1%)
Somnolence	0	1 (2%)	0	0
Stupor	0	0	0	1 (1%)
Syncope	0	1 (2%)	0	0
Tremor	0	0	1 (1%)	0
Vasodilatation	0	0	0	1 (1%)

a   Subjects may have reported more than 1 adverse event leading to premature discontinuation, but were counted only once in the total.
*   Statistically significant difference versus the placebo treatment group (p≤0.05).
Cross Reference: Table 14.3.2__3 and Appendix 16.2__7.1.1

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12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Narratives for subjects who died, reported a serious adverse event, or prematurely discontinued from the study at least in part to an adverse event are presented in Section 14.3.3.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase (Table 14.3.2__1.1). Subject 4100 died on Day 79 due to a suicide attempt (COSTART term: suicide attempt) that the investigator considered to be unrelated to study drug.

Thirteen subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) reported 1 or more serious adverse events other than death. However, only 1 of these subjects (ABT-594 300 µg BID) reported an event considered to be probably related to study drug. This subject had a single episode of palpitation (COSTART term: palpitation) on Day 4 that resolved without further incident within 90 minutes. The remaining events were all considered to be not related or probably not related to study drug. Another 1 of the 13 subjects (ABT-594 300 µg BID) reported a serious adverse event (COSTART term: accidental injury [described as "status post fall down stairs"]) with onset >30 days after the last dose of study drug.

One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The overall incidence of subjects prematurely discontinuing due to adverse events was statistically significantly higher for the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups (28%, 46%, and 66%, respectively) than for the placebo treatment group (9%). Statistically significantly higher proportions of subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups prematurely discontinued study drug due to nausea (12%, 22%, and 30%, respectively) compared to subjects in the placebo treatment group (2%). Statistically significantly higher proportions of subjects in the ABT-594 225 µg and 300 µg BID treatment groups prematurely discontinued study drug

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due to dizziness (16% and 19%, respectively), vomiting (14% and 18%, respectively),
and abnormal dreams (9% and 10%, respectively) compared to subjects in the placebo
treatment group (0% each). A statistically significantly higher proportion of subjects in
the ABT-594 300 μg BID treatment group prematurely discontinued study drug due to
headache (12%) and asthenia (9%) compared to subjects in the placebo treatment group
(0% and 0%, respectively).

12.4   Clinical Laboratory Evaluation

12.4.1   Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

The location of clinical laboratory data is presented below.

Laboratory Assessment	Statistical Analyses Tables	Values of Potential Clinical Significance	Individual Subject Listing[a] Appendix
Hematology	14.3.4__1.1	14.3.4__3.1	16.2__8.2.1
	14.3.4__2.1	14.3.4__4.1	16.2__8.2.2
			16.2__8.2.3
			16.2__8.2.4
			16.2__8.2.5
Blood Chemistry	14.3.4__1.2	14.3.4__3.2	16.2__8.3.1
	14.3.4__2.2	14.3.4__4.2	16.2__8.3.2
			16.2__8.3.3
			16.2__8.3.4
			16.2__8.3.5
			16.2__8.3.6
Urinalysis	14.3.4__1.3	14.3.4__3.3	16.2__8.4.1
	14.3.4__2.3	14.3.4__4.3	16.2__8.4.2
			16.2__8.4.3
			16.2__8.4.4
			16.2__8.4.5

[a]   Baseline determinations are also presented in Appendix 16.2__4.

Laboratory normal reference ranges are presented in Appendix 16.2__8.1. Criteria for
potentially clinically significant laboratory values (i.e., very high or very low values) are
presented in Table 14.3.4__1.0.

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12.4.2   Evaluation of Each Laboratory Parameter

12.4.2.1   Laboratory Values Over Time

Hematology

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for hematology parameters is presented in Table 12.4a.

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Table 12.4a   Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Hematology Parameters

Hematology Parameter (units)	Placebo (N=62)[a]	ABT-594 150 µg BID (N=61)[a]	ABT-594 225 µg BID (N=66)	ABT-594 300 µg BID (N=62)
Hemoglobin (g/dL)				
Baseline Mean	14.10	13.80	13.81	14.02
Mean Change to Minimum	-0.46	-0.30	-0.21*	-0.09*
Hematocrit (%)				
Baseline Mean	40.95	40.39	40.11	40.82
Mean Change to Minimum	-1.06	-1.16	-0.79	-0.26*
Mean Change to Maximum	1.60	0.87	0.73*	0.90
RBC Count (x 10^{12}/L)				
Baseline Mean	4.66	4.61	4.58	4.70
Mean Change to Minimum	-0.13	-0.11	-0.05*	-0.05*
MCV (fL)				
Baseline Mean	88.24	87.79	87.65	87.26
Mean Change to Maximum	2.00	1.26	0.68*	1.24
MCH (pg)				
Baseline Mean	30.52	30.07	30.21	30.00
Mean Change to Minimum	-0.73	-0.30*	-0.33*	-0.27*
Mean Change to Final	-0.29	0.16*	-0.08	0.00
MCHC (g/dL)				
Baseline Mean	34.50	34.30	34.45	34.47
Mean Change to Minimum	-1.08	-0.46*	-0.47*	-0.52*
Platelet Count (x 10^9/L)				
Baseline Mean	246.70	250.27	253.70	241.32
Mean Change to Minimum	-10.98	-13.27	-7.82	4.05*
Mean Change to Maximum	29.33	14.15*	10.89*	26.84
WBC Count (x 10^9/L)				
Baseline Mean	8.01	7.60	7.36	6.95
Mean Change to Minimum	-0.51	-0.50	-0.03*	0.02*
Neutrophils (%)				
Baseline Mean	61.01	62.82	61.86	60.62
Mean Change to Minimum	-2.25	-2.39	-0.60	0.09*
Lymphocytes (%)				
Baseline Mean	30.04	28.78	29.70	30.53
Mean Change to Maximum	2.08	2.17	0.63	0.02*
Eosinophils (%)				
Baseline Mean	2.90	2.32	2.38	2.53
Mean Change to Minimum	-0.82	-0.50	-0.34*	-0.60
Mean Change to Maximum	0.41	0.32	0.29	-0.05*

* Statistically significant difference versus the placebo treatment group (p≤0.05).
[a] N=60 for Platelet Count only

Table 12.4a   Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Hematology Parameters (continued)

| Hematology Parameter (units) | Treatment Group | | | |
| | Placebo (N=60) | ABT-594 | | |
		150 µg BID (N=59)	225 µg BID (N=65)	300 µg BID (N=61)
Prothrombin Time (sec)				
Baseline Mean	12.30	12.33	12.20	12.79
Mean Change to Maximum	0.39	0.15	0.08*	0.25
Activated Partial Thromboplastin Time (sec)				
Baseline Mean	24.32	24.69	25.11	25.53
Mean Change to Maximum	1.60	0.72	0.57*	0.27*
Mean Change to Final	0.56	-0.13	-0.24	-0.53*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.4__1.1 and Appendices 16.2__8.2.1 through 16.2__8.2.5

Blood Chemistry

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for blood chemistry parameters is presented in Table 12.4b.

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Table 12.4b   Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Blood Chemistry Parameters

Blood Chemistry Parameter (units)	Treatment Group			
	Placebo (N=62)	ABT-594		
		150 µg BID (N=61)	225 µg BID (N=66)	300 µg BID (N=62)
Glucose (mg/dL)				
Baseline Mean	175.68	192.13	169.09	183.90
Mean Change to Maximum	57.79	44.36	39.39	17.94*
Total Protein (g/dL)				
Baseline Mean	7.25	7.24	7.31	7.26
Mean Change to Maximum	0.19	0.14	0.03*	0.13
Mean Change to Final	0.03	-0.06	-0.13*	0.00
Total Bilirubin (mg/dL)				
Baseline Mean	0.40	0.43	0.38	0.36
Mean Change to Minimum	-0.05	-0.07	-0.04	-0.00*
Alkaline Phosphatase (IU/L)				
Baseline Mean	75.94	78.74	81.88	74.35
Mean Change to Maximum	4.27	1.43	-0.14*	1.95
SGOT/AST (IU/L)				
Baseline Mean	22.35	21.87	23.70	22.81
Mean Change to Maximum	2.76	1.56	-1.32*	0.84
SGPT/ALT (IU/L)				
Baseline Mean	23.08	24.11	24.65	26.42
Mean Change to Maximum	3.69	0.79	-1.44*	0.08
Sodium (mEq/L)				
Baseline Mean	141.18	139.82	140.85	140.16
Mean Change to Minimum	-2.77	-1.59	-1.92	-0.87*
Potassium (mEq/L)				
Baseline Mean	4.55	4.41	4.53	4.38
Mean Change to Minimum	-0.32	-0.15*	-0.19	-0.15*
Chloride (mEq/L)				
Baseline Mean	104.37	102.56	103.32	102.23
Mean Change to Minimum	-3.00	-1.15*	-1.95	-1.34*
Mean Change to Final	-0.71	0.80*	-1.00	0.29
Bicarbonate (mEq/L)				
Baseline Mean	26.42	26.72	27.10	27.57
Mean Change to Maximum	1.26	0.33*	0.71	0.61
Calcium (mg/dL)				
Baseline Mean	9.51	9.46	9.57	9.51
Mean Change to Minimum	-0.33	-0.17*	-0.21	-0.07*
Inorganic Phosphorus (mg/dL)				
Baseline Mean	3.64	3.71	3.72	3.56
Mean Change to Minimum	-0.42	-0.27	-0.11*	-0.11*
* Statistically significant difference versus the placebo treatment group (p≤0.05).				

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Table 12.4b   Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Blood Chemistry Parameters (continued)

| Blood Chemistry Parameter (units) | Placebo (N=62) | Treatment Group | | |
| | | ABT-594 | | |
		150 µg BID (N=61)	225 µg BID (N=66)	300 µg BID (N=62)
Cholesterol (mg/dL)				
Baseline Mean	190.44	199.54	204.95	203.79
Mean Change to Maximum	12.71	4.44*	-1.05*	0.21*
Mean Change to Final	1.27	-3.66	-8.55*	-5.53
Triglycerides (mg/dL)				
Baseline Mean	239.31	274.03	277.55	300.03
Mean Change to Maximum	80.69	42.26	28.77*	-7.34*
Mean Change to Final	39.32	-9.11*	-3.59	-36.23*

* Statistically significant difference versus the placebo treatment group (p≤0.05).

Cross Reference: Table 14.3.4__1.2 and Appendices 16.2__8.3.1 through 16.2__8.3.5

Urinalysis

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for urinalysis is presented in Table 12.4c.

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Table 12.4c   Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Urinalysis Parameters

Urinalysis Parameter (units)	Treatment Group			
		ABT-594		
	Placebo (N=61)	150 µg BID (N=58)	225 µg BID (N=65)	300 µg BID (N=62)
Urine pH				
Baseline Mean	5.75	5.59	5.51	5.68
Mean Change to Minimum	-0.67	-0.36*	-0.26*	-0.19*
Mean Change to Final	-0.34	-0.12	-0.09	0.00*
Specific Gravity				
Baseline Mean	1.02	1.02	1.02	1.02
Mean Change to Minimum	-0.004	-0.003	-0.002	-0.001*
* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).				

Cross Reference: Table 14.3.4__1.3 and Appendices 16.2__8.4.1 through 16.2__8.4.4

12.4.2.2   Individual Subject Changes

The percentage of subjects with shifts in laboratory parameters from baseline to the final value using potentially clinically significant criteria to define categories are presented in Table 14.3.4__2.1 for hematology variables, Table 14.3.4__2.2 for blood chemistry variables, and Table 14.3.4__2.3 for urinalysis variables. The majority of subjects had clinical laboratory values within normal range at the Baseline and Final Visits.

12.4.2.3   Individual Clinically Significant Abnormalities

Hematology Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant hematology values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.4__4.1. The percentages of subjects who had hematology values that met the potentially clinically significant criteria were generally similar among the treatment groups. None of these values were associated with premature discontinuations. The percentages of subjects who developed

hematology values that met the potentially clinically significant criteria are presented in Table 12.4d; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

Table 12.4d   Number and Percentage of Subjects with Hematology Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
			ABT-594		
		Placebo	150 µg BID	225 µg BID	300 µg BID
Hemoglobin	High: ≥18.5 g/dL (males) ≥16.5 g/dL (females)	(N=54) 1 (2%)	(N=50) 0	(N=45) 0	(N=34) 0
Hematocrit	Low: ≤37% (males) ≤32% (females)	(N=49) 4 (8%)	(N=47) 3 (6%)	(N=42) 4 (10%)	(N=32) 0
RBC	Low: ≤3.8 x 10^{12}/L (males) ≤3.5 x 10^{12}/L (females)	(N=53) 0	(N=50) 0	(N=45) 1 (2%)	(N=34) 0
WBC	High: ≥16.0 x 10^9/L	(N=56) 0	(N=51) 0	(N=45) 0	(N=34) 1 (3%)

Cross Reference: Table 14.3.4__4.1 and Appendices 16.2__8.2.1 through 16.2__8.2.5

Individual subjects with hematology values that met the potentially clinically significant criteria are presented in Table 14.3.4__3.1.

Blood Chemistry Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant blood chemistry values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.4__4.2. The percentages of subjects who had blood chemistry values that met the potentially clinically significant criteria were generally similar among the treatment groups. One subject (4246) in the ABT-594 300 µg BID treatment group had a very high glucose on Day 14 (334 mg/dL) and was prematurely discontinued from study drug due to hyperglycemia. However, the

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subject's glucose was high (229 mg/dL) at baseline, indicating poor control of her
diabetes. The percentages of subjects who developed blood chemistry values that met
the potentially clinically significant criteria are presented in Table 12.4e; only those
parameters that had at least 1 subject who met the potentially clinically significant
criteria are presented.

**Table 12.4e   Number and Percentage of Subjects with Blood
Chemistry Values Meeting Potentially Clinically
Significant Criteria (All Treated Subjects)**

		Treatment Group n (%)			
			ABT-594		
Variable	**Criteria**	**Placebo**	**150 μg BID**	**225 μg BID**	**300 μg BID**
Glucose		(N=33)	(N=23)	(N=28)	(N=20)
	High: ≥175 mg/dL	19 (58%)	16 (70%)	16 (57%)	7 (35%)
	Low: ≤45 mg/dL	0	1 (4%)	0	0
Uric Acid		(N=56)	(N=51)	(N=42)	(N=34)
	High: ≥10.5 mg/dL (males) ≥8.5 mg/dL (females)	0	0	0	1 (3%)
BUN		(N=56)	(N=51)	(N=43)	(N=34)
	High: ≥30 mg/dL	2 (4%)	1 (2%)	0	1 (3%)
Creatinine		(N=57)	(N=51)	(N=45)	(N=35)
	High: ≥2.0 mg/dL	0	1 (2%)	0	0
Chloride		(N=57)	(N=51)	(N=45)	(N=35)
	Low: ≤90 mEq/L	1 (2%)	0	0	0
Calcium		(N=57)	(N=51)	(N=45)	(N=35)
	Low: ≤8.2 mg/dL	1 (2%)	0	0	0
Triglycerides		(N=54)	(N=43)	(N=40)	(N=34)
	High: ≥600 mg/dL	2 (4%)	0	2 (5%)	1 (3%)

Cross Reference: Table 14.3.4__4.2 and Appendices 16.2__8.3.1 through 16.2__8.3.5

Individual subjects with blood chemistry values that met the potentially clinically
significant criteria are presented in Table 14.3.4__3.2.

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Urinalysis Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant urinalysis values are presented in
Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting
these criteria is presented in Table 14.3.4__4.3. The percentages of subjects who had
urinalysis values that met the potentially clinically significant criteria were generally
similar among the treatment groups. None of these values were associated with
premature discontinuations. The percentages of subjects who developed urinalysis
values that met the potentially clinically significant criteria are presented in
Table 12.4f; only those parameters that had at least 1 subject who met the potentially
clinically significant criteria are presented.

**Table 12.4f   Number and Percentage of Subjects with Urinalysis
                 Values Meeting Potentially Clinically Significant
                 Criteria (All Treated Subjects)**

| | | Treatment Group n (%) | | | |
| | | | ABT-594 | | |
Variable	Criteria	Placebo	150 µg BID	225 µg BID	300 µg BID
Urine Glucose	High: ≥3+ a	(N=50) 12 (24%)	(N=44) 12 (27%)	(N=41) 10 (24%)	(N=27) 5 (19%)
Urine Protein	High: ≥3+ a / ≥10	(N=56) 0	(N=50) 0	(N=45) 0	(N=32) 1 (3%)
Urine Ketones	High: ≥3+ a	(N=57) 1 (2%)	(N=50) 0	(N=45) 0	(N=32) 0
Urine RBCs	High: ≥8/hpf (male) ≥10/hpf (female)	(N=57) 2 (4%)	(N=50) 3 (6%)	(N=44) 0	(N=31) 2 (6%)
Urine WBCs	High: ≥10/hpf/≥ 2+	(N=55) 4 (7%)	(N=50) 2 (4%)	(N=45) 3 (7%)	(N=32) 4 (13%)

hpf = high power field.

a ≥3+ on a scale with 4+ being the maximum value.

Cross Reference: Table 14.3.4__4.3 and Appendices 16.2__8.4.1 through 16.2__8.4.4

Individual subjects with urinalysis values that met the potentially clinically significant
criteria are presented in Table 14.3.4__3.3.

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12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1 Listing of Individual Measurements by Subject and Each Abnormal Value

The location of vital sign, physical findings, and safety data is presented below.

Assessment	Statistical Analyses Tables	Values of Potential Clinical Significance	Individual Subject Listing Appendix
Physical Examination	None	None	16.2__4.4
Vital Signs	14.3.5__1	14.3.5__2	16.2__9.1
		14.3.5__3	
ECGs	14.3.6__1	14.3.6__3	16.2__9.2
	14.3.6__2	14.3.6__4	

No normal reference range was used for evaluating vital sign or ECG variables. Criteria for potentially clinically significant values (i.e., Very High or Very Low values) for vital signs and ECG are presented in Table 14.3.4__1.0.

12.5.2 Findings on Physical Examination

Clinically significant deteriorations from baseline physical examination were captured as adverse events (Appendices 16.2__4.4 and 16.2__7.1.1).

12.5.3 Vital Signs Evaluation

12.5.3.1 Vital Signs Values Over Time

Statistically significant differences were observed between treatment groups for mean change from baseline to minimum and/or maximum; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for vital sign parameters is presented in Table 12.5a.

Table 12.5a   Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Vital Sign Parameters

| | Treatment Group | | | |
| | | ABT-594 | | |
Vital Sign Parameter (units)	Placebo (N=62)	150 µg BID (N=62)	225 µg BID (N=66)	300 µg BID (N=64)
Systolic Blood Pressure (mm Hg)				
Baseline Mean	130.8	134.3	136.8	133.9
Mean Change to Maximum	11.8	8.6	3.9*	7.6
Diastolic Blood Pressure (mm Hg)				
Baseline Mean	76.3	78.7	77.6	76.5
Mean Change to Maximum	6.4	4.5	2.7*	4.6
Mean Change to Final	1.4	-3.2*	-1.5	0.8
Heart Rate (bpm)	(N=62)	(N=61)	(N=66)	(N=63)
Baseline Mean	76.1	75.4	75.2	76.1
Mean Change to Final	2.5	-1.8*	2.0	0.6
Weight (pounds)	(N=61)	(N=60)	(N=62)	(N=60)
Baseline Mean	204.0	199.8	199.1	204.1
Mean Change to Minimum	-0.1	-2.1*	-1.9*	-2.8*
Mean Change to Maximum	1.8	0.0*	-0.1*	-1.4*
Mean Change to Final	1.1	-0.8*	-1.0*	-2.0*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.5__1 and Appendix 16.2__9.1

12.5.3.2   Individual Subject Changes

Criteria for potentially clinically significant vital signs and weight values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.5__3. The percentages of subjects who had vital signs values that met the potentially clinically significant criteria were generally similar among the treatment groups. A very high sitting systolic blood pressure value was reported by 0 placebo-treated subjects, 6% (3/50) of ABT-594 150 µg-treated subjects, 0 ABT-594 225 µg-treated subjects, and 3% (1/36) of ABT-594 300 µg BID-treated subjects (Table 14.3.5__3).

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12.5.4   Electrocardiogram Evaluation

12.5.4.1   ECG Values Over Time

No statistically significant differences were observed between placebo and any of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value for ECG variables (Table 14.3.6__1).

12.5.4.2   Individual Clinically Significant Abnormalities

The percentage of subjects with shifts in ECG parameters from baseline to the final value using potentially clinically significant criteria to define categories are presented in Table 14.3.6__2. The majority of subjects had ECG values within normal range at the Baseline and Final Visits.

12.5.4.3   Individual Clinically Significant Abnormalities

Criteria for potentially clinically significant ECG values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.6__4. The percentages of subjects who had ECG values that met the potentially clinically significant criteria were generally similar among the treatment groups. Of note, the high QT_C interval in an ABT-594 225 µg BID-treated subject (4081) was an isolated occurrence that was not associated with an adverse event. The percentages of subjects who developed ECG values that met the potentially clinically significant criteria are presented in Table 12.5b; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

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**Table 12.5b   Number and Percentage of Subjects with ECG Values
Meeting Potentially Clinically Significant Criteria (All
Treated Subjects)**

Variable	Criteria	Treatment Group n (%)			
			ABT-594		
		Placebo	150 µg BID	225 µg BID	300 µg BID
QT$_C$ Interval[a]		(N=49)	(N=41)	(N=30)	(N=21)
	High: ≥500 msec	0	0	1 (3%)	0
PR Interval		(N=44)	(N=41)	(N=30)	(N=20)
	High: ≥210 msec	1 (2%)	0	1 (3%)	0
Heart Rate		(N=50)	(N=41)	(N=31)	(N=21)
	High: ≥120 bpm and increased ≥30 bpm from baseline	0	0	2 (6%)	0
[a] QT$_C$ calculated as QT divided by the square root of RR interval.					

Cross Reference: Table 14.3.6__4 and Appendix 16.2__9.2

Individual subjects with ECG values that met the potentially clinically significant
criteria are summarized in Table 14.3.6__3.

12.6   Safety Conclusions

Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91%
of subjects receiving ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported
treatment-emergent adverse events. The overall incidence of adverse events was
statistically significantly higher for each of the ABT-594 treatment groups than for the
placebo treatment group. The most frequently reported (≥10% of subjects in any
ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness,
vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had
statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and
46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%,
22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared
to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A
statistically significantly greater proportion of subjects in the ABT-594 225 µg and

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300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%,
respectively) compared to subjects in the placebo treatment group (2%). Subjects in the
placebo treatment group had a statistically significantly greater incidence of treatment-
emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment
group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg
BID) died 58 days after completion of the Treatment Phase. The subject died due to
suicide, which the investigator considered to be unrelated to study drug. In addition to
the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and
4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these
subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID)
reported serious adverse events associated with the cardiovascular system during the
study. Each subject had multiple risk factors for cardiovascular disease. One hundred
subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg
BID) prematurely discontinued study drug due to 1 or more adverse events. The most
frequently reported (≥10% of subjects in any ABT-594 treatment group) adverse events
leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting,
abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time
and individual clinically significant for laboratory evaluations, vital signs, ECGs, and
physical examinations, were unremarkable for all treatment groups.

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13.0   Discussion and Overall Conclusions

ABT-594 at 150 μg, 225 μg, and 300 μg BID was statistically significantly superior to
placebo for the primary efficacy variable, the mean change from baseline to final for the
average diary-based Pain Rating Scale. Furthermore, the mean improvement from
baseline to final for the average site-based Pain Rating Scale score was statistically
significantly superior in each of the ABT-594 treatment groups compared to placebo.
Statistically significant linear dose responses were observed in the model that included
the placebo treatment group for mean change from baseline to final for the average diary-
and site-based Pain Rating Scale scores.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment
groups had at least a 50% improvement in either their average diary- or site-based Pain
Rating Scale scores at the final evaluation compared to subjects in the placebo treatment
group.

There were no statistically significant differences between the placebo treatment group
and any of the ABT-594 treatment groups for the mean change from baseline to final in
the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline
to final in SF-36™ Health Status Survey, a statistically significant improvement was
observed for the ABT-594 225 μg BID treatment group in the physical component
summary compared to the placebo treatment group. However, statistically significant
worsening was observed for the ABT-594 300 μg BID treatment group in the mental
component summary compared to the placebo treatment group.

Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91%
of subjects receiving ABT-594 150 μg, 225 μg, and 300 μg BID, respectively, reported
treatment-emergent adverse events. The overall incidence of adverse events was
statistically significantly higher for each of the ABT-594 treatment groups than for the
placebo treatment group. The most frequently reported (≥10% of subjects in any
ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness,
vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

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Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg and 300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time and individual clinically significant for laboratory evaluations, vital signs, ECGs, and physical examinations, were unremarkable for all treatment groups.

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Summary of Anticipated Expert Testimony by Dr. Bruce E. Rodda

The following is a summary of the anticipated expert testimony of Dr. Bruce E. Rodda in connection with the action entitled <u>John Hancock Life Insurance Company, John Hancock Variable Life Insurance Company, and Manulife Insurance Company (f/k/a Investors Partner Insurance Company) v. Abbott Laboratories</u>, U.S.D.C. (Mass.) Civil Action No. 05-11150-DPW. Dr. Rodda has been asked by Munger, Tolles & Olson LLP, on behalf of Abbott Laboratories, to provide the Court with expert testimony regarding the development of new pharmaceutical compounds, including without limitation, the statistical aspects of evaluating and interpreting the results of clinical trials in support of these developmental activities. Dr. Rodda's testimony may include, inter alia, expert testimony regarding the Abbott study referred to as ABT-Protocol M99-114, A Randomized, Double-Blind Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy.

Dr. Rodda is the Principal of Strategic Statistical Consulting, LLC, a firm that provides statistical consulting to the pharmaceutical and biotechnology industries. He is also Adjunct Professor of Biostatistics at the University of Texas. Dr. Rodda received a B.A. in mathematics from Alfred University, an M.S. and Ph.D. in Biostatistics from Tulane University, and an M.B.A. from Fairleigh Dickinson University. After receipt of his Ph.D., Dr. Rodda spent more than 30 years in the pharmaceutical industry, working for Eli Lilly, Merck, Ayerst Laboratories, Bristol-Myers Squibb, Schering-Plough, PPD Development, and Pharmacia. At Eli Lilly, Dr. Rodda was the senior statistician in Lilly's clinical research efforts. He left Eli Lilly to join Merck, where he was in charge of

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biostatistics and data management for all Merck's development studies that were conducted outside the U.S., leaving Merck as Senior Director of this organization. During his tenure at Ayerst Laboratories, Dr. Rodda led Technical Operations for the company, which included statistics, data management, clinical operations (clinical trial field monitoring staff), and clinical systems. At Bristol-Myers Squibb, Dr. Rodda was responsible for all statistics and data management activities for the company on a global basis. Dr. Rodda then joined Schering-Plough as Vice President of Research Administration, a position in which he directed several functions, among them being statistics, data management, medical writing, and project management. He then joined PPD Development as Vice President for Operations, Americas. In this role, Dr. Rodda directed statistics, data management, and clinical operations for all North and South American operations for a large contract research organization. After a short period on the faculty of Texas State University, he returned to the industry with Pharmacia, serving as head of Medical Development Strategy until Pharmacia's acquisition by Pfizer in 2003. In this position, he was responsible for the strategic, financial, organizational, and administrative operations of the global clinical development organization. During his career in the industry, Dr. Rodda held adjunct academic appointments at Indiana University, The University of Illinois, The Rockefeller University, and Texas State University. In 2003 he established Strategic Statistical Consulting, LLC and joined The University of Texas as Adjunct Professor of Biostatistics. Dr. Rodda has been honored by being elected a Fellow of the American Statistical Association, being awarded a Commissioner's Special Citation by the Commissioner of the Food and Drug Administration, and being awarded a Career Achievement Award by the Pharmaceutical

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Research and Manufacturers of America.   Dr. Rodda is author or co-author of

approximately 70 publications and has presented approximately 50 papers at scientific

meetings. Copies of Dr. Rodda's current C.V., a summary of his industrial experience,

and a selection of his scientific publications are appended to this summary as Exhibits 1,

2, and 3, respectively.

Dr. Rodda's anticipated testimony is expected to include opinions regarding the

anticipated testimony of Dr. Barry Gold. Pursuant to the agreement of the parties to this

action, this summary of Dr. Rodda's anticipated expert testimony does not include Dr.

Rodda's expected opinions regarding statistical issues, including without limitation his

expected opinions regarding the anticipated testimony of Dr. Barry Gold relating to

statistical issues. Dr. Rodda's opinions regarding statistical issues raised by Dr. Gold will

be included in the summary of Dr. Rodda's anticipated expert testimony regarding

plaintiffs' expected anticipated expert testimony of plaintiffs' expert, Dr. William

Fairweather, which has not yet been provided to Abbott or to Dr. Rodda. If, for any

reason, plaintiffs do not prepare and/or serve on Abbott the anticipated expert testimony

of Dr. Fairweather, Dr. Rodda will address statistical issues, including those raised by Dr.

Gold, in a supplement to the present summary of Dr. Rodda's anticipated testimony.

Dr. Rodda will testify based upon his own experience, using information and

materials available in the public domain (including, but not limited to, information from

the United States Food and Drug Administration's ("FDA") website and the European

Medicines Agency ("EMEA") website), and upon testimony and materials obtained in

discovery in this action. During his testimony, Dr. Rodda may make reference to specific evidence contained in documents or witness testimony.

Dr. Rodda is being compensated on an hourly basis for the work that he performs in this matter. His billing rate is $350 per hour plus expenses, and his compensation is unrelated to the outcome of this litigation. Dr. Rodda has not testified as an expert at trial or by deposition within the preceding four years.

The opinions and analysis contained in this summary of Dr. Rodda's anticipated testimony are based on currently available information. Dr. Rodda's work is continuing and he plans to analyze any new information, including any such new information that may be provided in Dr. Fairweather's expected report and/or at the depositions of Dr. Gold and Dr. Fairweather. Dr. Rodda may modify this summary in light of such new information. The present summary of Dr. Rodda's anticipated testimony may be supplemented by his deposition testimony.

Dr. Rodda is expected to opine on Dr. Gold's anticipated testimony regarding the development of new therapeutic agents in the pharmaceutical industry. Dr. Rodda is expected to opine on areas in which he feels Dr. Gold's anticipated testimony is incorrect, incomplete, or unclear. Some of the comments that Dr. Rodda is expected to make in this regard are as follows, with citations to Dr. Gold's anticipated testimony (DGAT).

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DGAT, p. 4, lines 8 -14: Dr. Gold states that a goal of Phase I studies is to gain early evidence of efficacy, if possible. Because most Phase I studies are conducted in normal volunteers and not patients with the condition of interest, it is not usually possible to obtain evidence of effectiveness in Phase I studies. The exceptions to this generalization are Phase I studies involving oncology agents, where the adverse events often associated with such agents may make the administration of these agents to normal volunteers unacceptable. Many Phase I studies in oncology agents are therefore conducted in patients with the conditions of interest, providing an opportunity to obtain preliminary evidence of efficacy. Dr. Gold also opines that the total number of subjects included in Phase I studies is between 20 and 80. While the number of subjects included in any single Phase I study is small, the requirement to estimate tolerance, determine pharmacokinetics, obtain preliminary pharmacology information, and estimate bioavailability and bioequivalence often requires that the aggregate number of subjects in all the Phase I studies for any particular agent be much larger.

DGAT, p. 4, lines 19 – 20: Dr. Gold is correct in his assertion that the FDA does not use, nor has defined, the Phase IIa and Phase IIb nomenclature. For this and other reasons, many companies also do not use this nomenclature, referring only to Phase II for these studies. Because of this lack of definition, different companies may use this distinction in different ways or make no distinction of this kind.

DGAT, p. 5, line 7: Dr. Gold is correct in his contention that Phase III studies in many indications often require very large numbers of patients. However, Dr. Rodda is

expected to opine that studies in cancer and rare diseases are usually conducted in smaller numbers of patients. This may be for a variety of reasons. Large studies are necessary to detect relatively small therapeutic advances and are needed to provide a basis for characterizing the safety profile of a new product. In contrast, the benefit/risk ratio in cancer patients is large for modest advances (benefit), and adverse events (risk) that would not be acceptable in less serious conditions than cancer are acceptable in cancer patients. An additional practical reason that some Phase III studies are relatively small is that large numbers of patients with a relatively rare disease are not available for study.

DGAT, p. 5, line 20: Dr. Gold refers to a "typical" timetable for initiating clinical trials. Dr. Rodda is expected to opine, however, that many factors are involved in the timing of initiating a clinical trial and that different companies may use different timetables for initiating clinical trials, depending on a variety of factors, including availability of investigational material, resources, corporate strategy, and regulatory considerations.

DGAT, p. 6, line 3: Dr. Gold's use of the term "typical" for the planning, structure, and operation of clinical trials is simplistic and incorrectly suggests that companies share a common approach in this area. Dr. Rodda is expected to opine that different companies have different planning processes and may approach implementation of clinical trials differently.

DGAT, p. 6, line 6: Dr. Gold's use of the phrase "types and significance of both positive and negative clinical data and results" is unclear. The term "significance" is often used to mean clinically important, to suggest statistical significance, or to refer to the study's impact on the sponsor. Dr. Rodda is expected to opine that each of these meanings is different from the others. The term "negative" may also have several meanings when referring to the results of a clinical trial. Two such interpretations might be that a study is inconclusive or that a study is conclusive, but does not support the desired outcome. These are very different cases.

DGAT, p.6, line 7: Dr. Gold states that clinical trials are usually designed by a clinical monitor. Dr. Rodda is expected to opine that this assertion is incorrect. In most companies, clinical trials are designed by a multidisciplinary team, not by a clinical monitor. According to ICH E-6 (ICH Good Clinical Practice Guidelines), "The sponsor should utilize appropriately qualified individuals (e.g., biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports."

DGAT, p. 6, lines 7 – 9: Dr. Gold uses the term "monitor" in two ways, without distinguishing between the two. One definition appears to characterize a senior level physician who has some authority over the study (refer to the previous comment). Dr. Rodda is expected to opine that the term "monitor" as defined in this way is used less frequently than it was a decade or more ago. The ICH Good Clinical Practice Guidelines

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(ICH E-6) clearly define the responsibilities of a clinical monitor. As defined in the guidelines, the term "monitor" refers to the act of monitoring in the field, usually performed by a clinical research associate (CRA). The roles of a senior level physician and a CRA are very different and are held by individuals with very different training. The roles and responsibilities of a clinical monitor are specified in detail in the ICH Good Clinical Practices Guidelines (E6, Section 5.1).

DGAT, p. 6, line 12 – 16: Contrary to Dr. Gold's assertion that a sponsor may initiate a study if the FDA does not object within 30 days following submission of a protocol, Dr. Rodda is expected to opine that this statement is correct only for the first study submitted with an application for an Investigational New Drug (IND) exemption. While protocols for subsequent studies are submitted to the FDA, no other studies fall under this 30 day review concept. (21CFR312.40). As the FDA states in its "Overview of the FDA Role in the Development of Therapeutics for Cancer", "All protocols under an IND are submitted to the FDA, but unlike the initial studies, the sponsor does not have to wait for an approval from the FDA to begin a new protocol." See fda.gov/cder/cancer/docs/overview.html,

DGAT, p.6, last line: Dr. Gold contends that investigators are not paid for their expertise in participating in a clinical research effort, but are only reimbursed for expenses and record keeping. Dr. Rodda is expected to opine that although payment to investigators may go through a university or clinic administration, the investigators are paid for their participation in a clinical trial. Highly respected investigators command

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higher grants than investigators who are not as well known or influential. Note that on page 15, line 3 of DGAT, Dr. Gold states that a sponsor may "offer a financial incentive to the investigators" to improve slow enrollment. Often the purpose of such financial incentives is to encourage an investigator with competing studies to enroll patients in the study for which he/she receives the most money. Such incentives are usually unrelated to operating expenses and record keeping.

DGAT, p. 7, line 15 – 18: Dr. Gold states that a local IRB reviews trials run by a private practice physician. Dr. Rodda is expected to opine that if a study is run by a private practice physician or private group, the IRB does not need to be local. There are many professional IRBs that perform their function for clinical sites that do not have their own IRBs. Geographic proximity is not important.

DGAT, p. 7, line 21 – 22: Contrary to Dr. Gold's contention that "any observations made outside the study variables usually are considered irrelevant to the study results", Dr. Rodda is expected to testify that observations made outside the defined study variables are always documented and reported. Handwritten comments in margins of case report forms are routinely included in the sponsor's database. All information that is collected is considered relevant to the results of the study, even if it was unanticipated. Patient safety and well-being is always primary and such comments are not ignored.

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DGAT, p. 9, lines 1 – 4: Dr. Gold states that a trial that is terminated prior to completion such that the data do not have the desired statistical significance generally is not regarded in the pharmaceutical industry as a "successful" trial. Dr. Rodda is expected to opine that this is not necessarily the case. A clinical trial may be terminated prior to its originally planned conclusion for several reasons. A "successful" trial is one that is definitive, not necessarily one that is supportive of the desired result. Although a sponsor would like each of its trials to be supportive of the ideal outcome of bringing a new product to the market, it also does not want to unnecessarily invest in a product that will not be safe and effective, nor expose patients in clinical trials to an experimental therapy unnecessarily. Termination of a trial can thus be viewed as "successful" if the trial is definitive. Therefore, a clinical trial that provides a conclusive result, while not the outcome desired (and perhaps not achieving "statistical significance") may be considered a "successful" trial.

DGAT, p. 9, line 7: Dr. Gold contends that members of a project team are temporarily assigned to report to a project team leader. Dr. Rodda is expected to discuss that in many companies employees retain their functional reporting relationships, but are assigned to work as a member of a project team. They do not "report to a project team leader". Maintaining functional reporting relationships is often desirable for a variety of reasons, including an employee's participation on several project teams and the need to have functional management triage their project responsibilities.

DGAT, p. 9, line 9: Dr. Gold's contention that membership in project teams is dynamic in many companies, with different disciplines being members at different stages of development is correct. However, in most companies, and according to ICH Good Clinical Practice Guidelines, a statistician is a primary and continuing member of a project team.

DGAT, p. 9, line 12 – 14: While Dr. Gold is correct that in some companies the development project teams may be contained within the clinical organization, Dr. Rodda is expected to testify that it is also the case that in many other companies, the multidisciplinary project teams report to management outside the clinical organization.

DGAT, p. 10, line 1 and preceding: Dr. Gold uses the terms, "adverse events" and "premature termination", in the same sentence and does not make clear that these terms have different meanings. Dr. Rodda is expected to opine that while a study may be terminated prematurely because of an unexpectedly large number of adverse events, studies may also be terminated prematurely for a variety of other reasons. The sponsor's primary responsibility is to the patient and it would be unethical to enroll patients in a trial where the risk outweighed the potential benefit. However, to terminate a trial prematurely, without allowing the study an opportunity to provide meaningful information could also be viewed as unethical for those patients in the trial.

DGAT, p. 10, line 5: It is the responsibility of the project personnel to apprise management of the progress of a program. However, Dr. Rodda is expected to opine that

the processes for apprising management of the progress of clinical trials vary from company to company. This information is often proprietary and not publicly available outside the company.

DGAT, p. 11, line 9: Dr. Gold asserts that there are 20 projects in Pfizer's clinical development pipeline. However, on 30 November 2006, Pfizer announced that it currently had 242 projects in 11 therapeutic areas.

DGAT, p. 12, line 10: Dr. Gold suggests that the clinical monitor can halt a study. Dr. Rodda is expected to opine that the scientific, ethical, and legal aspects of stopping a study prematurely dictate that premature termination of a clinical trial is decided at a high level within a company. It is not common for a clinical monitor to have the authority to halt a clinical trial.

DGAT, p. 12, line 12: In this section of his report Dr. Gold seems to equate adverse events and adverse reactions as "side effects". Dr. Rodda is expected to opine that adverse events and adverse reactions are not the same. Adverse reactions have an association with the therapy under study; adverse events do not necessarily have such an association. In addition, while adverse reactions may be referred to as "side effects", adverse events are not. According to the FDA Good Clinical Practice Guidelines (Federal Register, Vo. 62, No. 90, 9 May 1997) an adverse reaction is "Any noxious and unintended response to a medicinal product related to any dose." An adverse event is "Any untoward medical occurrence in a patient or clinical investigation subject

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administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment". The term "side effect" is not cited.

DGAT, p. 12, line 15: Dr. Gold refers to a "target profile". Dr. Rodda is expected to opine that different companies define this term in different ways. In addition, different companies use their target profiles or target product profiles for different purposes.

DGAT, p. 12, line 15 – 16: Although Dr. Gold contends that the study monitor discusses unexpected adverse events with their management, Dr. Rodda is expected to opine that in many clinical trials unexpected adverse events are not always discussed with management.

DGAT, p. 12, lines 16 – 19: In Dr. Gold's anticipated testimony, he contends that uncomfortable adverse events are likely to slow enrollment. However, since a patient must be enrolled to experience the uncomfortable adverse event, this is unlikely to be an issue on the patient level. On the investigator level, the investigator must view this as an ethical issue to justify blocking enrollment of potential patients or to justify enrolling them in a competing study. In such a case, the investigator has an obligation to inform both the sponsor and the IRB of his concerns. For studies with small numbers of patients on each treatment, this should not be an issue if the study is double blinded. There are many reasons for premature termination, including lack of efficacy, unacceptable safety, and poor enrollment. It is important to distinguish between stopping enrollment before

the target sample is acquired but then continuing enrolled patients to completion, versus completely halting the study at a particular point in time. While slow enrollment or excessive dropouts may result in premature stopping of enrollment, these reasons are not often the reasons for early termination of a trial. Slow enrollment is usually addressed by seeking mechanisms for improving enrollment, not by terminating a study prematurely. If an unexpectedly large number of dropouts were observed in a study, the underlying reasons for this would be explored before deciding what action to take. It would be uncommon for a sponsor to review blinded data to make a decision regarding early termination. The creation of an independent data safety monitoring board, with the authority to recommend continuation or termination, would be a less risky, more independent, and more credible way of reviewing the data in an unblinded fashion (the sponsor remains blinded).

DGAT, p. 12, last line: While Dr. Gold is correct that most Phase II and Phase III clinical trials are double blinded, few clinical trials in cancer are blinded or double blinded, because of the nature of oncology therapies.

DGAT, p. 13, line 4: Dr. Rodda is expected to opine that observational bias is always a potential factor in studies that are not double-blinded. Dr. Gold asserts that blinding provides a means of guarding against observational bias. Blinding refers to the patient's ignorance of the therapy received, while double blinding includes the investigator's ignorance of the therapy, as well. Dr. Rodda is expected to opine that if a study is not double blinded, the opportunity for observational bias can be so great as to

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bring into question to the credibility of the study. If a study is not double blinded, one

must always be aware of the possibility of investigator bias.

DGAT, p. 13, line 7: As discussed above, Dr. Rodda is expected to opine that,

contrary to Dr. Gold's contention, blinding does not provide a means for guarding against

observational bias; rather, only double blinding provides a means for guarding against

observational bias.

DGAT, p. 13, line 11: Dr. Gold suggests that clinical study data are provided to

the clinical monitor. Dr. Rodda is expected to opine that, although in some companies

the clinical monitor may have primary responsibility for reviewing these data from a

medical perspective, the bulk of data are not sent directly to the clinical monitor. This

would be a slow and inefficient way of dealing with the large quantity of data associated

with a clinical trial, the bulk of which would not require medical judgment.

DGAT, p. 13, line 12: In this paragraph, Dr. Gold states that all demographic data

are reported to the company. He is certainly correct in this assertion. However, the

statement should be broadened to state that ALL data regarding the clinical study are

reported to the company.

DGAT, p. 13, line 15: Dr. Gold's reference to reporting adverse events on line

suggests that this is necessarily quicker than other means. Dr. Rodda is expected to opine

that reporting adverse events "on line" is a technical means of reporting. It does not

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relate to the currency of reporting. An adverse event observed a week ago may be reported "on line" today, if the investigator waited until today to report it.

DGAT, p. 13, lines 15 - 22: Dr. Rodda is expected to opine regarding Dr. Gold's opinion that a high number of adverse events may suggest that the results of a study might be negative. A high number of adverse events may suggest that a study has a high incidence of adverse events, not necessarily that the results will be negative. Adverse events are characteristic of pharmacologic agents. One purpose of clinical studies is to estimate the incidence of adverse events and to characterize their distribution in the population. It is not the intent of most studies to minimize the occurrence of a phenomenon that may be associated with the therapy under study. An important objective in any clinical trial is to characterize the adverse event profile in the population under study.

Studies of serious illnesses usually have high incidences of adverse events and do not imply any likelihood that the study will be negative. Most phase III studies use an intent-to-treat analysis as the primary analysis. Dr. Gold's reference to the relationship between the intent-to-treat concept and a high incidence of adverse events and a likelihood of negative results is unclear.

Dr. Rodda is expected to opine that it is not likely that a study will be halted prematurely unless the results are known and understood (i.e., unblinded), the number of patients enrolled is close enough to the original target so the reduction in power is

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acceptable to the sponsor, or that other factors outside the trial dictate its early termination (e.g., information from other trials/sources).

Dr. Rodda is also expected to opine that using blinded information for making determinations to terminate enrollment prematurely is uncommon. The adverse event profile can vary substantially from study to study, even for the same product and similar protocol designs. If an experimental agent has a unique adverse event, observing an excess of this event in a blinded summary can be misleading if the underlying patterns of adverse events confound an ability to absolutely distinguish active therapy from control on this basis. The risks of terminating an expensive study on incomplete (i.e., blinded) information is a risk that most companies do not choose to take. The possibility of inconclusive or incorrect decisions, the loss of money and time, and the ethical issue of enrolling patients in an inconclusive study are all reasons against stopping a study prematurely based on blinded data. For example, consider a study that is designed to compare a placebo (P) with two doses (low – L and high H) of an agent that is thought to be associated with an increased incidence of headache. If the study were conducted according to the protocol and evaluated in an unblinded manner at the study's conclusion, the relationship between the treatments and the incidence of headache could be determined.

However, if one attempted to use blinded results at an interim analysis to form a judgment regarding the relationship between headache and the three treatments, it would

not be possible to distinguish among the following cases (among others): P=L=H, P=L<H, and P<L<H.

Consider a specific example of the above issue where information from previous studies suggests a 10% incidence of headache associated with the agent and that P, L, and H are studied in a trial of 300 patients (100 per treatment group). Suppose an interim analysis was conducted when the study is 50% complete (i.e. 50 patients per group) and a headache incidence of 20 % was observed (i.e., higher than expected). A blinded review of the results at this point would be unable to distinguish among the following three cases: P=10, L=10, H=10; P=5, L=5, H=20; and P=0, l=10, H=20. Thus, the blinded review could not distinguish among the cases where all treatments were the same; L is similar to P, but H has a high incidence of headache; and the case where there is an increasing association of headache with dose. Blinded evaluation would not reveal any of these patterns and making decisions based on such a blinded interim analysis could be misleading. For this reason, blinded review of interim clinical trail data is not commonly performed.

Dr. Rodda is also expected to opine regarding this issue with respect to Study ABT-594, M99-114. He is expected to testify that Study ABT-594, M99-114 was designed to enroll 320 patients. Despite prolonging enrollment and investigating methodologies for increasing patient enrollment, the study was terminated after enrolling 269 patients. These patients were uniformly allocated among the four treatment groups according to the randomization schedule. The study was run to conclusion, either to the

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point a patient withdrew or to the scheduled final visit for each patient. The study was

not terminated prematurely.

Dr. Rodda is expected to opine that while the sample size of 269 patients was

somewhat less than the planned sample size, completing studies with fewer than the

originally planned number is common, since anticipated enrollment is often more than

what is actually achieved in clinical trials. In general, if a sponsor feels that either patient

safety and/or ethics might require early termination of a clinical trial, they will employ a

Data Safety Monitoring Board of independent scientists to evaluate unblinded data. That

committee would then recommend continuing the study according to the protocol or

terminating the study. Unless their recommendation is to terminate the study, the sponsor

would remain blinded to the results of the study.

DGAT, p. 14, lines 5 – 10: Dr. Gold asserts that the responsibility of a CRA is to

ensure that each investigator maintains a CRF, that the CRF is current, and that the data

entered into the CRF is in accord with the primary documents in the patient records. Dr.

Rodda is expected to opine that Dr. Gold has minimized the true responsibility of a CRA.

A CRA has many more responsibilities than those cited in this paragraph of Dr. Gold's

anticipated testimony. In fact, ICH E-6 (ICH Good Clinical Practice Guidelines)

provides 3 single spaced pages describing the goals, training, and responsibilities of

CRAs. The principal responsibility of a CRA (monitor) is to ensure that the investigator

conducts the study according to the protocol in all areas.

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DGAT, p. 14, lines 12 – 14: Dr. Gold suggests that electronic data capture ("EDC") provides demographic and adverse event data to the sponsor in real time. Dr. Rodda is expected to opine that while this is certainly possible, EDC is not limited to demographic and adverse event data nor does it imply instantaneous receipt of data from the moment of collection. Many investigators will collect data for days and then enter it into an EDC system when they have available time. In this case, data are not available instantaneously.

DGAT, p. 14, p. 17: Dr. Gold's comment that "some protocols are written to restrict or exclude what are referred to as "co-morbidities" suggests that such a process may compromise a clinical trial. Dr. Rodda is expected to opine that this, in fact, strengthens a clinical trial and permits a clearer understanding of the underlying mechanism. Many, if not most, Phase II and III studies restrict inclusion of patients with various co-morbidities. This allows clear definition of the population for which the treatment might be used and reduces the confounding effect that the co-morbidities might create when interpreting the results of the study. Dr. Gold's reference to rumors affecting enrollment addresses a totally different concept. In most studies, prospective patients do not know nor speak with one another. Since neither they nor the investigator would ordinarily know what the patient is taking, increasing the rate of dropouts or decreasing the rate of enrollment for this reason would not be common.

DGAT, p. 15, line 11: Dr. Rodda is expected to opine that if a contract research organization is responsible for the data management of the study, the data are returned to the contract research organization, rather than the sponsor.

DGAT, p. 15, line 13: Dr. Rodda is expected to opine that data are reviewed, queried, cleaned, returned to the investigator, and re-entered on an ongoing basis, not at the end of the trial. It would be very inefficient to accumulate data until the end of a trial.

DGAT, p. 15, line 19: Dr. Gold is expected to testify that before and during a compound's clinical development, senior R&D management defines a variety of Go/No-Go decisions. While management does consider a variety of Go/No-Go decision points, the actual decision rules can rarely be defined explicitly. The acceptable outcomes of a clinical program will often vary depending on corporate priorities, the competitive environment, and the fit of a potential product with the company's portfolio.

DGAT, p. 16, line 6: Dr. Gold opines that by deviating from a once daily target, ABT-773 "fell short". Dr. Rodda is expected to opine that a target product profile is, by definition, a target. Literally all drugs will "fall short" of the target in some way. This in no way indicates that they are not potentially valuable therapeutic advances.

DGAT, p. 16, lines 9 – 12: Dr. Rodda may opine that Dr. Gold's position that companies begin to develop backup compounds when a compound is or is about to be terminated is incorrect. Backup compounds are often developed concurrently with or

slightly behind the lead compound(s). The development of backup compounds often begins without knowledge of the ultimate success of the original candidate. The benefit of backup compounds is not to salvage a failed compound, but to provide an alternative, perhaps superior, compound. This would provide positive options to the company even if the initial compound was positive by providing two compounds in the class or a candidate for out-licensing. Since backup compounds can benefit from the lessons learned from earlier compounds, they are often more successful than earlier compounds in development.

DGAT, p. 17, lines 5 – 7: Dr. Rodda is expected to opine that companies are constantly evaluating and re-evaluating their product portfolios against their corporate objectives. Since few, if any companies, are capable of filling their development pipeline with compounds discovered internally, companies are constantly considering in-licensing candidates to augment their portfolio and out-licensing candidates that may not fit with their corporate strategy. Dr. Gold seems to suggest that if a company has a compound that "runs into difficulty" they would out-license it. Dr. Rodda is expected to opine that, if a compound runs into difficulty, the company may not consider out-licensing because the problems encountered will be known to the potential out-licensing partner. The implication of Dr. Gold's anticipated testimony that problem candidates are out-licensed is not well founded.

Dr. Rodda is expected to opine that the clinical protocol for Study ABT-594, Protocol M99-114 possessed, inter alia, the following positive attributes. The objectives

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of the protocol were clearly described and the variables upon which these objectives would be evaluated were clearly presented. A plan for the statistical evaluation of the principal variables was presented in the protocol. The protocol was a complete document and was consistent with good clinical practice (GCP) guidelines, International Conference on Harmonization (ICH) guidelines, and the recommendations contained in the Declaration of Helsinki (protection of patients).

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References

1. European Medicines Agency: Scientific Guidelines for Human Medicinal Products: ICH E6 – Guideline for Good Clinical Practices. 1996.

2. European Medicines Agency: Scientific Guidelines for Human Medicinal Products: ICH E9 – Statistical Principles in Clinical Trials. 1998.

3. The World Medical Association: World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. 2004

4. 21 CFR 312.40 General requirements for use of an investigational new drug in a clinical investigation

EXHIBIT 1

June 2006

Bruce E. Rodda, Ph.D., M.B.A.

Curriculum Vitae

PERSONAL

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EDUCATION

M.B.A. - Fairleigh Dickinson University, Teaneck, NJ, 1982
(Thesis title: The Impact of Governmental Regulations Governing Transborder
Data Flow on Multinational Pharmaceutical Companies)

Ph.D., Biostatistics - Tulane University, New Orleans, LA, 1969
(Dissertation title: An Analytic System for the Statistical Analysis of Markov
Chains)

M.S., Biostatistics - Tulane University, New Orleans, LA, 1967

B.A., Mathematics - Alfred University, Alfred, NY, 1965

Other universities attended from which course credit was received:

Bucknell University
Yale University
Louisiana State University
Indiana University
Somerset County Community College
Bucks County Community College

INDUSTRIAL POSITIONS HELD

1969-1973   Senior Statistician, Lilly Research Laboratories
Eli Lilly and Company, Indianapolis, IN

1974-1976   Research Scientist, Lilly Research Laboratories
Eli Lilly and Company, Indianapolis, IN

1976-1977   Associate Director, Clinical Biostatistics and Research Data Systems
International, Merck Sharp and Dohme Research Laboratories
Merck and Company. Rahway, NJ

1977-1982   Director, Clinical Biostatistics and Research Data Systems International
Merck Sharp and Dohme Research Laboratories
Merck and Company, Rahway, NJ

1982-1987   Senior Director, Clinical Biostatistics and Research Data Systems
International, Merck Sharp and Dohme Research Laboratories
Merck and Company, Rahway, NJ

1987-1988   Vice President, Clinical Operations
Ayerst Laboratories, New York, NY
and
Assistant Vice President, Overseas Clinical Operations
Wyeth-Ayerst Research, Philadelphia, PA
Both companies are divisions of American Home Products, Inc.

1988-1994   Vice President, Biostatistics and Data Management
Bristol-Myers Squibb Pharmaceutical Research Institute,
Princeton, NJ

1994-1997   Vice President, Research Administration
Schering-Plough Research Institute, Kenilworth, NJ

1998-1999   Vice President, Operations-Americas
PPD Development, Austin, TX

2001-2003   Global Head, Medical Development Strategy
Pharmacia Corporation, Peapack, NJ

2003-   Principal, Strategic Statistical Consulting LLC
Spicewood, TX

ACADEMIC POSITIONS HELD

1965-1967   NIH (General Medical Sciences) Trainee and Teaching Assistant,
            Tulane University Medical School, New Orleans, LA

1967-1968   Statistical Research Assistant, Biostatistics Department,
            Tulane University Medical School, New Orleans, LA

1968-1969   Public Health Service Predoctoral Research Fellow,
            Tulane University Medical School, New Orleans, LA

1972-1974   Instructor, Department of Pharmacology and Toxicology,
            Indiana University Medical School, Indianapolis, IN

1975-1976   Assistant Professor,
            Department of Pharmacology and Toxicology,
            Indiana University Medical School, Indianapolis, IN

1977-1978   Guest Investigator,
            The Rockefeller University, New York, NY

1979-1990   Assistant Professor of Community Medicine,
            University of Illinois School of Medicine, Rockford, IL

1991-1998   Member, Industrial Advisory Committee
            Rutgers University, New Brunswick, NJ
            (Chair 1995-1998)

2000-   Professor of Clinical Research and Biostatistics,
            Texas State University, San Marcos, TX

2005 -   Adjunct Professor of Biostatistics, The University of Texas School of
            Public Health, The University of Texas Health Science Center at Houston,
            Houston, TX

In addition to academic appointments, invited seminars have been presented at:

American University   Louisiana State University
University of Connecticut   McNeese State University
Indiana University Medical Center   Columbia University
University of Illinois Medical school at Chicago   University of Buffalo
University of Illinois Medical School at Rockford   Rutgers University
Medical University of South Carolina   Food and Drug Administration
University of Massachusetts

MISCELLANEOUS POSITIONS HELD

1973-1976   Consultant to the Veterans Administration Hospital in Indianapolis, IN and the Veterans Administration Hospital in Shreveport, LA

1975   Consultant -- Indianapolis Department of Education

1979   Guest Faculty -- Epidemiology Survey Course -- Sponsored by the University of Illinois School of Medicine

2000   Member, Advisory Panel -- U.S. Food and Drug Administration

2004 - 2005   Member, Scientific Advisory Board, Daiichi Medical Research, Inc.

Consultant to NIH Special Study Sections:

1. Human health effects of polybrominated biphenyls
2. Immunotoxicology of environmental agents
3. Response surface methodology in cancer chemotherapy
4. Genetic and environmental factors in disease
5. Clinical and postmortem evaluation of Alzheimer's disease
6. Computer systems for clinical trials
7. Information networks for cognitive scientists

Personal presentations have been made to the pharmaceutical regulatory agencies of:

Sweden
Belgium
Spain
England
Canada
United States

RESEARCH INTERESTS

Experimental design, general statistical methodology, and pharmacokinetic modeling.

PROFESSIONAL ASSOCIATIONS

International Society of Clinical Biostatistics

American Statistical Association
      Fellow (Elected 1991)
      Member Bioavailability Committee, 1971-1972
      Executive Committee, Biopharmaceutical Section, 1991-1994
      Chair, Biopharmaceutical Section, 1993-1994
      Executive Committee, Princeton-Trenton Chapter, 1994
      Chair, Corporate Representatives Committee, 1996-1999

Biometric Society
      Member, Regional Advisory Board, 1986-1988

Fellow, Royal Statistical Society
Chartered Statistician, Royal Statistical Society

Drug Information Association

American Society for Clinical Pharmacology and Therapeutics
      Vice Chairman, Section on Biostatistics and Clinical Trial Methodology, 1986-1989
      Chairman, Council III (Biostatistics and Clinical Trial Methodology, Medico-Legal
            Matters, and R&D Administration), 1987-1988
      Board of Directors, 1987 - 1988

Society for Clinical Trials
      Nominating Committee, 1992-1994 (Chair-1994)

Society of the Sigma XI

Delta Mu Delta (National Business Honorary)

Listed in American Men and Women of Science

Listed in Who's Who in the East

Editorial Board -- Controlled Clinical Trials, 1983-1987

Editorial Board -- Journal of Chronic Diseases, 1975-1987

Editorial Board -- Journal of Clinical Epidemiology, 1988 - present

PROFESSIONAL ASSOCIATIONS (continued)

Associate Editor -- Journal of the American Statistical Association, Biopharmaceutical Statistics, Special Applications Section, 1989

Editorial Advisory Board -- Pharmaceutical Medicine, 1988 - 1991

Editorial Board -- Journal of Biopharmaceutical Statistics, 1990 - 1997

Pharmaceutical Research and Manufacturers of America (formerly Pharmaceutical Manufacturers Association)
    Biostatistics Subsection
        Member, Steering Committee, 1981 - 1985
        Chairman, Long Range Planning Committee, 1982 - 1984
        Vice Chairman, 1983 - 1984
        Chairman, 1984 - 1985
        Advisor, 1986 - 1988
    Member, Ad Hoc Committee on Drugs in the Elderly, 1983 - 1988
    Member, Bioavailability/Bioequivalence Committee, 1985 - 1988
    Member, Biostatistics Guidelines Committee, 1985 - 1986
    Member, PMA/FDA/ASCPT Committee on Drug Level Monitoring, 1985 - 1988
    Member, Bioavailability Guidelines Committee, 1985 - 1986
    Member, PMA/FDA Joint Committee on Computerized Biopharmaceutics
        Submissions, 1987 - 1990
    Member, Ad Hoc Committee on ANDA Regulations, 1989

Recipient of FDA Commissioner's Special Citation (CANDA Guidance Task Force), 1993

Recipient of PhRMA Career Achievement Award, 2002

PUBLICATIONS

1. Rodda, B.E.: "An Analytic System for the Statistical Analysis of Markov Chains." Ph.D. Dissertation, Tulane University, 1969. University Microfilms, Ann Arbor, MI (1969).

2. Rodda, B.E. and Miller, M.C.: "Analysis and Simulation of Biological Processes Using Finite Markov Chains." Biometrics 25:201 (1969) (Abstract).

3. Wolen, R.L. and Rodda, B.E.: "Automated Determination of Protein Binding by Ultrafiltration." The Pharmacologist, 12:244 (1970) (Abstract).

4. Kiplinger, G.F.; Manno, J.E.; Rodda, B.E.; and Forney, R.B.: "Dose-Response Analysis of the Effects of Tetrahydrocannabinol in Man." Clin. Pharmacol. Ther., 12:650-657 (1971).

5. Rodda, B.E.; Scholz, N.E.; Gruber, C.M.; and Wolen, R.L.: "Evaluation of Plasma Concentration of Propoxyphene Utilizing a Hybrid Principal Components -- Analysis of Variance Technique: Case I -- Equimolar Doses." Toxicol. Appl. Pharmacol., 19:563-571 (1971).

6. Rodda, B.E.; Scholz, N.E.; Gruber, C.M.; and Wolen, R.L.: "Evaluation of Plasma Concentration of Propoxyphene Utilizing a Hybrid Principal Components -- Analysis of Variance Technique: Case II -- Equipotent Doses." Toxicol. Appl. Pharmacol., 19:572-582 (1971).

7. Rodda, B.E.; Miller, M.C.; and Bruhn, J.G.: "Prediction of Anxiety and Depression Patterns Among Coronary patients Using a Markov Chain Analysis." Behavioral Sci., 16:482-489 (1971).

8. Crabtree, R.E.; Young, E.C.; Galloway, J.A.; and Rodda, B.E.: "The Use of Highly Purified 'Single Component' Insulins in Insulin Resistance" Diabetes, 20:352 (1971) (Abstract).

9. Matsuda, A.; Galloway, J.A.; Diller, E.R.; Rodda, B.E.; and Young, E.C.: "The Effect of Weight Change and Sulfonylurea Treatment on Circadian Blood Glucose and Serum Insulin in Maturity Onset Diabetes." Diabetes, 20:366 (1971) (Abstract).

10. Rodda, B.E.: "Sustained Release Preparations: Estimation of Plasma Concentration in the One Compartment Open Model When Release is Both Immediate and Zero Order." Arch. Int Pharmacodyn., 194:290-296 (1971).

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PUBLICATIONS (continued)

11. Rubin, A.; Rodda, B.E.; Warrick, P.; Rudolfo, A.S.; and Gruber, C.M.: "Physiologic Disposition of Fenoprofen in Man: I - Pharmacokinetic Comparison of the Calcium and Sodium Salts Administered Orally." J. Pharm. Sci., 60:1797-1801 (1971).

12. Rubin, A.; Rodda, B.E.; Warrick, P.; Rudolfo, A.S.; and Gruber, C.M.: "Physiologic Disposition of Fenoprofen in Man: II - Plasma and Urine Pharmacokinetics After Oral and Intravenous Administration." J. Pharm. Sci., 61:739-745 (1972).

13. Manno, J.E.; Kiplinger, G.F.; Rodda, B.E.; Forney, R.B.; and Manno, B.R.: "Dose-dependent Alterations in Human Motor and Mental Performance After Smoking Marijuana Cigarettes." Drug Addiction, Vol. II, Futura Publishing Co., Mt. Kisco, NY (1972).

14. Chernish, S.M.; Wolen, R.L.; and Rodda, B.E.: "Adsorption of Propoxyphene Hydrochloride by Activated Charcoal." Clinical Toxicology, 5:317-329 (1972).

15. Chernish, S.M.; Rubin, A.; Rodda, B.E.; Ridolfo, A.S.; and Gruber, C.M.: "Physiologic Disposition of Fenoprofen in Man: IV - The Effects of Position of Subject, Food Ingestion, and Antacid Ingestion on the Plasma Levels of Orally Administered Fenoprofen." J. Med., 3:249-257 (1972).

16. Martz, R.; Brown, D.J.; Forney, R.B.; Bright, T.P.; Kiplinger, G.F.; and Rodda, B.E.: "Propranolol Antagonism of Marijuana Induced Tachycardia." Life Sciences, 11:999-1006 (1972).

17. Martz, R.; Sonday, F.L.; Rodda, B.E.; Brown, D.J.; Kiplinger, G.F.; and Forney, R.B.: "The Effects of Marijuana on Auditory Thresholds." J. Aud. Res., 12:146-148 (1972).

18. Rubin, A.; Rodda, B.E.; Warrick, P.; Gruber, C.M.; and Ridolfo, A.S.: "Interactions of Aspirin with Nonsteroidal Anti-inflammatory Drugs in Man." Arthritis Rheum., 16:635-645 (1973).

19. Miller, R.E.; Chernish, S.M.; Rosenak, B.D.; and Rodda, B.E.: "Hypotonic Duodenography with Glucagon." Radiology, 108:35-42 (1973).

20. Lemberger, L.; Martz, R.; Rodda, B.E.; Forney, R.B.; and Rowe, H.: "Comparative Pharmacology of Delta-9-THC and its Metabolite, 11-OH-9-THC." J. Clin. Inv., 52:2411-2417 (1973).

PUBLICATIONS (continued)

21. Chernish, S.M.; Miller, R.E.; Rosenak, B.D.; Skucas, J.; and Rodda, B.E.: "Hypotonic Duodenography: A Double-blind Comparison of Glucagon to Placebo and to Two Anticholinergics." Gastroenterology, 64:709 (1973) (Abstract).

22. Evans, M.A.; Martz, R.; Rodda, B.E.; Brown, D.J.; Kiplinger, G.F.; Lemberger, L.; and Forney, R.B.: "Impairment of Performance with Low Doses of Marijuana." Clin. Pharmacol. Ther., 144:936-940 (1973).

23. Trygstad, C.W.; Bang, N.U.; Heidenreich, R.O.; Csiscko, B.M.; and Rodda, B.E.: "A Controlled Trial of Aspirin in Childhood Glomerular Disorders." Thrombos. Diasthes. Haemorrh. 30:12-16 (1973).

24. Evans, M.A.; Martz, R.; Rodda, B.E.; Brown, D.J.; Lemberger, L.; and Forney, R.B.; "Effects of d-Amphetamine on Psychomotor Skills." The Pharmacologist, 15:219 (1973) (Abstract).

25. Job, D.D.; Griffing, W.J.; and Rodda, B.E.: "A Possible Origin of Intestinal Gradients and Their Relation to Motility." Am. J. Physiol., 226:1510-1515 (1974).

26. Evans, M.A.; Martz, R.; Rodda, B.E.; Kiplinger, G.F.; and Forney, R.B.: "Quantitative Relationship Between Blood Alcohol Concentration and Psychomotor Performance." Clin. Pharmacol. Ther., 15:253-260 (1974).

27. Miller, R.E.; Chernish, S.M.; and Rodda, B.E.: "Cholecystography: A Cost Reduction Study." Radiology, 110:61-65 (1974).

28. Beall, A.C., et al: "The Development and Introduction of New Cardiovascular Drugs." Am. J. Cardiology, 34:457-486 (1974).

29. Miller, R.E.; Chernish, S.M.; Skucas, J.; Rosenak, B.D.; and Rodda, B.E.: Hypotonic Roentgenography with Glucagon." Am. J. Radiol., 121:264-274 (1974).

30. Gruber, C.M.; Waife, S.O.; and Rodda, B.E.: "Should Clinical Evaluation of Analgesia be Based on Single Doses? -- Some Pharmacokinetic Considerations." Clin. Pharmacol. Ther., 15:208 (1974) (Abstract).

31. Helleberg, L.; Rubin, A.; Wolen, R.L.; Rodda, B.E.; Ridolfo, A.S.; and Gruber, C.M.: "A Pharmacokinetic Interaction in Man Between Phenobarbitone and Fenoprofen, A New Anti-inflammatory Agent." Brit. J. Clin. Pharm., 1:371-374 (1971).

PUBLICATIONS (continued)

32. Rodda, B.E.: "Sequential Analysis in Phase 1 and Phase 2 Clinical Trials." in McMahon, F.G. (ed.) <u>Principles and Techniques of Human Research and Therapeutics. Vol IV - Importance of Experimental Design</u>, Futura Publishing Co., Mt. Kisco, NY (1974).

33. Wolen, R.L.; Rubin, A.; Rodda, B.E.; Ridolfo, A.S.; and Gruber, C.M.: "Problems Associated with Bioavailability and Dosage Regimen Studies in Man." <u>J. Pharmacokinetics and Biopharmaceutics</u>, 2:365-377 (1974)

34. Kiplinger, G.F.; Sokol, G.; and Rodda, B.E.: "Effect of Combined Alcohol and Propoxyphene on Human Performance." <u>Arch. Int. Pharmacodyn.</u>, 212:175-180 (1974).

35. Miller, R.E.; Chernish, S.M.; Skucas, J.; Rosenak, B.D.; and Rodda, B.E.: "Hypotonic Colon Examination with Glucagon." <u>Radiology</u>, 113:555-561 (1974).

36. Dalton, W.; Martz, R.; Lemberger, L.; Rodda, B.E.; and Forney, R.B.: "Clinical Effects of Marijuana Combined with Secobarbital." <u>Clin. Pharmacol. Ther.</u> 18:298-304 (1975).

37. Waife, S.O.; Gruber, C.M.; Rodda, B.E.; and Nash, J.F.: "Problems and Solutions to Single-Dose Testing of Analgesics: Comparison of Propoxyphene, Codeine, and Fenoprofen." <u>Internat. J. Clin. Pharmacol.</u>, 12:301-304 (1975).

38. Rodda, B.E.: "Multiclinic and Multi-investigator Trials of Cardiovascular Agents -- A Statistical Enigma." <u>Biometrics</u>, 31:600 (1975) (Abstract).

39. Nash, J.F.; Bechtol, L.D.; Lowary, L.R.; Rodda, B.E.; and Rose, H.A.: "The Relationship Between the Particle Size of Dicumarol and its Bioavailability in Dogs: Part I - Capsules." <u>Drug Development Communications</u>, 1:443-458 (1975).

40. Rodda, B.E.; Sampson, C.B.; and Smith, D.W.: "The One Compartment Open Model: Some Statistical Aspects of Parameter Estimation." <u>J. Roy. Stat. Soc. Series C</u>, 24:309-318 (1975).

41. Dalton, W.S.; Martz, R.; Rodda, B.E.; Lemberger, L.; and Forney, R.B.: "Combined Effects of Delta-9-Tetrahydrocannabinol and Cannabidiol in Man." <u>Forensic Science</u>, 5: 118 (1975). (Abstract)

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42. Cockerill, E.M.; Miller, R.E.; Chernish, S.M.; McLaughlin, G.C.; and Rodda, B.E.: "Optimal Visualizaion of Esophageal Varices." American J. Roentgenol. Rad. Therapy and Nuclear Med., 126: 516-523 (1976).

43. Dalton, W.S.; Martz, R.; Lemberger, L.; Rodda, B.E.; and Forney, R.B.: "The Influence of Cannabidiol on the Effects of Delta-9-Tetrahydrocannabinol in Man." Clin. Pharmacol. Ther. 19: 300-309 (1976).

44. Evans, M.A.; Martz, R.; Lemberger, L.; Rodda, B.E.; and Forney, R.B.: "Effects of Dextroamphetamine on Psychomotor Skills." Clin. Pharmacol. Ther., 19: 777-781 (1976).

45. Rodda, B.E.; Chernish, S.M.; and Nash, J.F.: "Pharmacokinetic Method of Designing Sustained Release Formulations - Propoxyphene Hydrochloride." J. Pharmacokinetics and Biopharmaceutics, 4: 243-253 (1976).

46. Rodda, B.E.; Chernish, S.M.; and Nash, J.F.: "Delayed Release Propoxyphene - Pharmacokinetic Design." Clin. Pharmacol. Ther., 19: 114 (1976) (Abstract).

47. Waife, S.O.; Gruber, C.M.; Rodda, B.E.; and Nash, J.F.: "Analgesia, Plasma Levels and Dosage of Propoxyphene." Int. J. Clin. Pharmacol., 13: 177-181 (1976).

48. Lemberger, L.; Dalton, W.; Martz, R.; Rodda, B.E., and Forney, R.B.: "Clinical Studies on the Interaction of Psychopharmacologic Agents with Marijuana." Annals N.Y. Academy Sci., 281: 219-228 (1976).

49. Rubin, A.; Chernish, S.M.; Crabtree, R.; Gruber, C.M.; Helleberg, L.; Rodda, B.E.; Warrick, P.; Wolen, R.L.; and Ridolfo, A.S.: "A Profile of the Physiological Disposition and Gastrointestinal Effects of Fenoprofen in Man." Curr. Med. Res. Opin., 2: 529-544 (1974).

50. Evans, M.A.; Martz, R.; Wimbish, G.; Griffis, L.; Rodda, B.E.; Brown, D.J.; Lemberger, L.; and Forney, R.B.: "Subjective Response and Excretion Patterns of Dextroamphetamine after the Administration of Therapeutic Doses." J. Forensic Sci., 2: 197-201 (1977).

51. Evans, M.A.; Martz, R.; Rodda, B.E.; Lemberger, L.; and Forney, R.B.: "Effects of Marijuana-Dextroamphetamine Combination." Clin. Pharmacol. Ther., 20: 350-358 (1976).

PUBLICATIONS (continued)

52. Dalton, W.S.; Martz, R.; Rodda, B.E.; Lemberger, L.; and Forney, R.B.: "Influence of Cannabidiol on Secobarbital Effects and Plasma Kinetics." Clin. Pharmacol. Ther., 20: 695-700 (1976).

53. Forney, R.B.; Martz, R.; Lemberger, L.; Rodda, B.E.; and Evans, M.A.: "The Combined Effect of Marijuana and Dextroamphetamine." Annals N.Y. Academy Sci., 281: 162-170 (1976).

54. Van Winzum, C. and Rodda, B.E.: "Diflunisal - Efficacy in Postoperative Pain." Br. J. Clin. Pharm., 4: 39S - 43S (1977).

55. Andrew, A.; Rodda, B.E.; Verhaest, L.; and Van Winzum, C.: "Diflunisal - Six Month Experience in Osteoarthritis." Br. J. Clin. Pharm., 4: 45S-52S (1977).

56. Kleber, J.W.; Galloway, J.A.; and Rodda, B.E.: "GLC Determination of Acetohexamide and Hydroxyhexamide in Biological Fluids." J. Pharm.Sci., 66: 635-638 (1977).

57. Nash, J.F.; Galloway, J.A.; Garner, A.D.; Johnson, D.W.; Kleber, J.W.; and Rodda, B.E.: "In Vivo and In Vitro Availability of Acetohexamide from Tablets." Can. J. Pharm. Sci. 12: 59-64 (1977).

58. Rodda, B.E. and Davis, R.L.: "Application of Bayesian Methods to the Evaluation of Data from Pharmacokinetic and Bioavailability Studies." Biometrics, 34: 534 (1978) (Abstract).

59. Rodda, B.E. and Davis, R.L.: "Determining the Probability of an Important Difference in Bioavailability." Clin. Pharmacol. Ther., 28: 247-252. (1980).

60. Rodda, B.E. and Huber, P.B.: "Statistical Considerations in Drug Absorption and Disposition Studies - Current Practices." Albert, K.S. (ed.) Statistical Considerations in Drug Absorption and Disposition Studies., A.Ph.A. Press (1980).

61. Rodda, B.E.: "Analysis of Sets of Estimates from Pharmacokinetic Studies." in Endreny, L. (ed.), Kinetic Data Analysis: Design and Analysis of Enzyme and Pharmacokinetic Experiments., Plenum Press, NY (1981).

62. Rodda, B.E.: "Consideracoes Biostatisticos no Desenho de Ensaios do Prevencao Secundaria do Infarto do Miocardio e Morte Subita." Gomes, A.J. ed., Anais do Symposio Internacional Sobre Infarto Myocardio, Unipress Editorial Ltda., Sao Paulo (1981).

PUBLICATIONS (continued)

63. Rodda, B.E.: "The Timolol Myocardial Infarction Study - An Evaluation of Selected Variables." Circulation, 67: 1101-1106 (1983).

64. Rodda, B.E.: "Pooled Inferences from Multiclinic Drug Trials." Biometrics, 39: 810 (1983). (Abstract).

65. Abrams, W.B. and Rodda, B.E.: "Clinical Trial Design - Industry Perspective." Cutler, N.R. (ed.), Methodological Concerns for Clinical Trials in Geriatrics., Plenum Press, NY (1986).

66. Rodda, B.E.; Tsianco, M.C.; Bolognese, J.A; and Kersten, M.K.: "Clinical Development." in Peace, K.E. (ed.), Biopharmaceutical Statistics for Drug Development, Marcel-Dekker, NY (1988).

67. Boissel, J.P., et al (The Beta-Blocker Pooling Project Research Group): "The Beta-Blocker Pooling Project (BBPP): Subgroup Findings from Randomized Trials in Post-Infarction Patients." Eur. Heart J., 9: 8-16 (1988).

68. Rodda, B.E.: "Bioavailability: Designs and Analysis." in Berry, D.A. (ed.), Statistical Methodology in Pharmaceutical Science, Marcel-Dekker, NY (1989).

69. Hwang, I.K. and Rodda, B.E.: "Interim Analysis in the Norwegian Multicenter Study." in Peace, K.E. (ed.), Biopharmaceutical Sequential Statistical Applications, Marcel-Dekker, NY (1991).

70. Rodda, B.E.; Brooks, C.; Reynolds, G.: Statistics and Clinical Trials." Clin. Pharmacol. Ther., 52: 104-105 (1992).

71. Waldo, A.L., et al: "Survival with Oral d-Sotalol in Patients with Left Ventricular Dysfunction after Myocardial Infarction: Rationale, Design, and Methods (the SWORD Trial)." Am. J. Cardiol., 75: 1023-1027 (1995).

72. Jukema, J.W., et al: "Effects of Lipid Lowering by Pravastatin on Progression and Regression of Coronary Artery Disease in Symptomatic Men with Normal to Moderately Elevated Serum Cholesterol Levels." Circulation, 91: 2528-2540 (1995).

73. Rodda, B.E.; Hajian, G.; Tsai, K.T.; Mellars, L.; and Capece, L.: "Analysis of 24-Hour Blood Pressure Data." J. Biopharm. Stat., 6(4): 495-513 (1996).

74. Rodda, B.E.; Millard, S.P.; and Krause, A.: "Statistics and the Drug Development Process" in Millard, S.P. and Krause, A. (ed.), Applied Statistics in the Pharmaceutical Industry, Springer-Verlag, Heidelberg (2001).

PUBLICATIONS (continued)

75. Williams, R.C., et al: "Treatment of Periodontitis by Local Administration of Minocycline Microspheres: A Controlled Trial." J. Periodontol., 72: 1535-1544 (2001).

PRESENTATIONS

1. Rodda, B.E. and Miller, M.C.: "An Analytic System for Finite Markov Chains." Presented at the VII Annual Symposium on Biomathematics and Computer Science in the Life Sciences, Houston, TX (March, 1969).

2. Rodda, B.E. and Miller M.C.: "Analysis and Simulation of Biological Processes Using Finite Markov Chains." Presented at the Joint Statistical Meetings (American Statistical Association, Biometric Society, Institute of Mathematical Statistics), New York, NY (August, 1969).

3. Rodda, B.E.: "Sequential Analysis of Clinical Trials." Invited lecture, Pharmaceutical Manufacturers Association training session for new industry physicians, Skytop, PA (April, 1972).

4. Rodda, B.E.: "Enumeration Data." Invited lecture, Pharmaceutical Manufacturers Association training session for new industry physicians, Skytop, PA (April, 1972).

5. Rodda, B.E.; Sampson, C.B.; and Smith, D.W.: "The One Compartment Open Model: Some Statistical Aspects of Parameter Estimation." Invited paper presented at the Joint Statistical Meetings (American Statistical Association, Biometric Society, Institute of Mathematical Statistics), Montreal, Quebec (August, 1972).

6. Rodda, B.E.: "Current Status of Sequential Design and Analysis of Clinical Trials." Invited paper presented to the Medical Section of the Pharmaceutical Manufacturers Association, Washington, DC (November, 1972).

7. Rodda, B.E.: "Sequential Design and Analysis in Phase I and Phase II Clinical Trials." Invited paper presented at the Symposium on Clinical Pharmacological Methods - Phase I and II, New Orleans, LA (March, 1973).

8. Rodda, B.E.: "Games People Play with Blood Level Curves." Presented to the Central Indiana Chapter, American Statistical Association, Indianapolis, IN (February, 1974).

9. Rodda, B.E.: "Multiclinic and Multi-investigator Trials of Cardiovascular Agents - A Statistical Enigma." Invited paper presented at the Joint Statistical Meetings (American Statistical Association, Biometric Society, Institute of Mathematical Statistics), St. Louis, MO (August, 1974).

10. Rodda, B.E.; Chernish, S.M.; and Nash, J.F.: "Delayed Release Propoxyphene - Pharmacokinetic Design." Presented at the annual meetings of the American Society of Clinical Pharmacology and Therapeutics, Seattle, WA (March, 1976).

PRESENTATIONS (continued)

11. Rodda, B.E. and Davis, R.L.: "Application of Bayesian Methods to the Evaluation of Data from Pharmacokinetic and Bioavailability Studies." Invited paper presented at the Biometric Society (ENAR) meetings, Lexington, KY (March, 1978).

12. Rodda, B.E. and Davis, R.L.: "Is There a Clinically Significant Difference? -- Answering the Right Question." Presented at the annual meeting of the American Society for Clinical Pharmacology and Therapeutics, Kansas City, MO (March, 1979).

13. Rodda, B.E. and Huber, P.B.: "Statistical Considerations in Drug Absorption and Disposition Studies." Presented at the annual meeting of the Academy of Pharmaceutical Sciences of the American Pharmaceutical Association, Washington, DC (April, 1980).

14. Rodda, B.E.: "Biostatistical Considerations in the Design of Secondary Prevention Trials of Myocardial Infarction and Sudden Death." Presented at the Simposio Internacional Sobre Infarto do Miocardio, Rio de Janiero, Brazil (May, 1981).

15. Rodda, B.E.: "International Statistical and Data Processing Support of Clinical Trials." Invited paper presented to the Pharmaceutical Manufacturers Association, Naples, FL (October, 1981).

16. Rodda, B.E.: "The Timolol Myocardial Infarction Study – An Evaluation of Selected Variables." Invited paper presented at the Symposium on the Implications of Recent Beta-blocker Trials for Post-MI Patients, Bethesda, MD (May, 1982).

17. Rodda, B.E.: "Multinational Clinical Trials: Organizational and Operational Considerations." Invited paper presented at the Conference on Changing Concepts in Bioavailability and Clinical Trials, Baltimore, MD (October, 1982).

18. Rodda, B.E.: "Problems of Inference in Multiclinic Trials." Invited paper presented at the annual meeting of the Biostatistics Subsection of the Pharmaceutical Manufacturers Association, New Orleans, LA (October, 1982).

19. Rodda, B.E.: "Sequential Methods in Clinical Trials." Invited paper presented to the annual meeting of the American Society for Clinical Pharmacology and Therapeutics, San Diego, CA (March, 1983).

20. Rodda, B.E.: "Pooled Inferences in Multiclinic Drug Trials." Invited paper presented at the Biometric Society (ENAR) meetings, Nashville, TN (March, 1983).

PRESENTATIONS (continued)

21. Rodda, B.E.: "Planning, Processing, and Quality Control of International Clinical Trials." Invited paper presented at the annual meeting of the Science Information Subsection of the Pharmaceutical Manufacturers Association, Tarpon Springs, FL (May, 1983).

22. Rodda, B.E.: "Statisticians in the U.S. Pharmaceutical Industry – Organization and Issues." Presented at the annual meeting of Statisticians in the Pharmaceutical Industry (U.K.), Bristol, England (September, 1983).

23. Rodda, B.E. "Foreign Clinical Trials – Design, Logistics, and Processing." Invited paper presented at the Medical Section meeting of the Pharmaceutical Manufacturers Association, Arlington, VA (November, 1983).

24. Rodda, B.E.: "Population Pharmacokinetics." Invited paper presented at the annual meeting of the American Society for Clinical Pharmacology and Therapeutics, Atlanta, GA (March, 1984).

25. Rodda, B.E.: "Concepts and Issues in Establishing Bioavailability and Bio-equivalence." Invited paper presented at the Midwest Pharmaceutical Statisticians Workshop, Muncie, IN (May, 1984).

26. Rodda, B.E.: "Statistical Considerations in Multinational Clinical Trials." Invited paper presented at the annual meeting of the Drug Information Association, San Diego, CA (June, 1984).

27. Rodda, B.E.: "Statistical Evaluation of Bioequivalence Trials." Invited paper presented at the annual meeting of the Drug Metabolism Discussion Group, Plymouth Meeting, PA (May, 1985).

28. Rodda, B.E.: "Clinical Data Management: A Domestic and International Perspective." Invited paper presented at the annual meeting of the Drug Information Association, Atlanta, GA (June, 1985).

29. Rodda, B.E.: "FDA Clinical and Statistical Guidelines." Invited presentation at the Drug Information Association meeting on the FDA Guidelines, Washington, DC (May, 1986).

30. Rodda, B.E.: "The Future of Statistics and Data Processing in Pharmaceutical Development." Invited paper presented at the Project Management Subsection meeting of the Pharmaceutical Manufacturers Association, Atlanta, GA (May, 1986).

PRESENTATIONS (continued)

31. Rodda, B.E.: "Statistical Considerations in Multinational Clinical Trials from the Perspective of a U.S. Sponsor." Invited paper presented at the annual meeting of the Pharmaceutical Manufacturers Association Biostatistics Subsection, Washington, DC (September, 1986).

32. Rodda, B.E.: "Pharmaceutical Industry Statisticians' Response to the FDA Statistical/Clinical Guidelines." Invited paper presented at the annual meeting of Statisticians in the Pharmaceutical Industry (U.K.), Southampton, England (September, 1986).

33. Rodda, B.E.: "Quantitative and Statistical Analysis of Data from Bioequivalence Studies." Testimony at the U.S. Food and Drug Administration Hearing on Bioequivalence of Solid Oral Dosage Forms, Washington, DC (September, 1986).

34. Rodda, B.E.: "Centralized and Distributed Data Entry and Data Processing of Foreign Clinical Trials." Invited presentation at the Pharmaceutical Manufacturers Association Data Processing Workshop, Washington, DC (September, 1986).

35. Rodda, B.E.: "An Overview of the Statistical Methodologies used in the Evaluation of Bioequivalence Studies." Invited presentation at the International Society of Clinical Biostatistics Meetings, Gothenburg, Sweden (September, 1987).

36. Rodda, B.E.: "Higher Opportunities for Statisticians in the Pharmaceutical Industry." Invited presentation at the Biometric Society (ENAR) meetings, Boston, MA (March, 1988).

37. Rodda, B.E.: "Update on the FDA Bioequivalence Task Force Recommendations." Invited presentation at the annual meeting of the Pharmaceutical Manufacturers Association Biostatistics Subsection, Clearwater, FL (October, 1988).

38. Rodda, B.E.: "Dose-Ranging Studies." Invited presentation at the Forty-fourth Annual Conference on Applied Statistics and Quality Control, Atlantic City, NJ (December, 1988).

39. Rodda, B.E.: "International Clinical Data Management - Global Centralization of a Logically Decentralized Function." Invited presentation at the Drug Information Association annual meetings, Washington, DC (June, 1991).

PRESENTATIONS (continued)

40. Rodda, B.E.: "Administrative Considerations Involved in Multinational Mergers of Data Management Departments." Invited presentation at the DIA Workshop on Technical and Organizational Challenges in Clinical Data Management, Noordwijk, The Netherlands (November, 1992).

41. Rodda, B.E.: "Harmonization and Opportunities for Cost Reduction in Multinational Clinical Development." Invited presentation at the DIA Annual Meeting, Chicago, IL (July, 1993).

42. Rodda, B.E.: "Regulatory Issues in Bioequivalence Studies." Presentation at the Joint Annual Statistics Meetings, San Francisco, CA (August, 1993).

43. Rodda, B.E.: "Generalized Estimating Equations in Longitudinal Data Analysis of Clinical Trials." Presentation at the Biometric Society Meetings (ENAR), Cleveland, OH (March, 1994).

44. Rodda, B.E.: "The Role of the Non-clinical Statistician in the Pharmaceutical Industry." Training program at the Joint Annual Statistics Meetings, Toronto, Canada (August, 1994) and at the Winter Statistics Meetings, Raleigh, NC (January, 1995) at the Joint Annual Statistics Meetings, Anaheim, CA (August 1997), and at the Joint Annual Statistics Meetings, Baltimore, MD (August, 1999).

45. Rodda, B.E.: "New Initiatives in the IND to NDA Process – The Paperless Future." Invited presentation to the Annual Meeting of the American Association of Pharmaceutical Sciences, Miami, FL (November, 1995).

46. Rodda, B.E.: "Statistical Considerations in 24-hour Blood Pressure Monitoring." Invited presentation to the Second Annual Biopharmaceutical Applied Statistics Symposium, San Diego, CA (December, 1995).

47. Rodda, B.E.: "Evolution of the Statistics Profession in the Pharmaceutical Industry." Invited presentation to the International Biometric Society Meeting (ENAR), Memphis, TN (March, 1997).

48. Rodda, B.E.: "Natural Selection or Intelligent Design – The Evolution of the Statistics Profession in the Pharmaceutical Industry." Keynote address, Midwest Biopharmaceutical Statisticians Workshop, Muncie, IN (May 2006).

EXHIBIT 2

Selected Publications

Bruce E. Rodda, Ph.D., M.B.A.

General

1. Rodda, B.E.: "Sequential Analysis in Phase 1 and Phase 2 Clinical Trials." in McMahon, F.G. (ed.) Principles and Techniques of Human Research and Therapeutics. Vol IV - Importance of Experimental Design, Futura Publishing Co., Mt. Kisco, NY (1974).

2. Beall, A.C., et al: "The Development and Introduction of New Cardiovascular Drugs." Am. J. Cardiology, 34:457-486 (1974).

3. Abrams, W.B. and Rodda, B.E.: "Clinical Trial Design - Industry Perspective." Cutler, N.R. (ed.), Methodological Concerns for Clinical Trials in Geriatrics., Plenum Press, NY (1986).

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EXHIBIT 3

August 2006

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SUMMARY OF INDUSTRIAL EXPERIENCE

PHARMACIA CORPORATION, PEAPACK, NJ

Global Head, Medical Development Strategy
2001 – 2003

Responsible for strategic, financial, organizational, and administrative elements of the global clinical development organization, approximately 1400 staff with an annual budget of $ 700 million.

PPD DEVELOPMENT, AUSTIN, TX

Vice President, Operations-Americas
1998-1999

Directed all clinical, statistical, and data management activities for clinical trials conducted under the aegis of PPD Development in North and South America. This entailed the integrated management of these functions, which comprised staffs of approximately 800 professionals at 10 locations and a top line business responsibility of approximately $200 million.

SCHERING-PLOUGH RESEARCH INSTITUTE, KENILWORTH, NJ

Vice President, Research Administration
1994-1997

Directed a multi-functional organization comprising research finance, capital projects, research support, laboratory animal care, information systems, project management, medical writing, statistics, and clinical data management. Full time staff of 400 professionals and an annual budget of $65 million.

SUMMARY OF INDUSTRIAL EXPERIENCE   (CONTINUED)

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE, PRINCETON, NJ

Vice President, Biostatistics and Data Management
1988-1994

Directed a multinational organization of statistics and clinical data management with an operating budget of $25 million and 250 staff located in New York, New Jersey, Connecticut, and Belgium.

AYERST LABORATORIES AND WYETH-AYERST RESEARCH, MADISON, NJ

Vice President, Clinical Operations (Ayerst) and Assistant Vice President, Regional Clinical Operations (Wyeth-Ayerst)
1987-1988

Directed worldwide clinical support of statistics, data management, computer support, and field monitoring staff for Ayerst, approximately 215 people. Following the merger of Ayerst into Wyeth, planned and staffed the ex-US infrastructure for these functions in Europe and Japan.

MERCK RESEARCH LABORATORIES, RAHWAY, NJ

Associate Director, Director, Senior Director of Biostatistics and Research Data Systems, International
1976-1987

Directed a department of approximately 50 staff in Europe and the United States in support of statistics and data management for all clinical studies conducted by Merck Research Laboratories outside the United States.

LILLY RESEARCH LABORATORIES, INDIANAPOLIS, IN

Senior Statistician/Research Scientist
1969-1976

Provided primary statistical input into Lilly's clinical research programs, including protocol development, statistical analysis, and FDA interaction.

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EDUCATION

- Fairleigh Dickinson University, Teaneck, NJ
  M.B.A. (Thesis Title: The Impact of Governmental Regulations Governing Transborder Data Flow on Multinational Pharmaceutical Companies)

- Tulane University, New Orleans, LA
  Ph.D., Biostatistics (Dissertation title: An Analytic System for the Statistical Analysis of Markov Chains)

- Tulane University, New Orleans, LA
  M.S., Biostatistics

- Alfred University, Alfred, NY
  B.A., Mathematics

PROFESSIONAL ACTIVITIES

Leadership positions in several statistical and clinical research societies. Fellow of the Royal Statistical Society, Chartered Statistician of the Royal Statistical Society, Fellow of the American Statistical Association.

Significant PhRMA activities, including membership on several committees, chairing the Biostatistical Subsection, and providing testimony to an FDA hearing on behalf of PhRMA. Recipient of PhRMA Career Achievement Award.

Extensive FDA and foreign regulatory experience in many therapeutic areas, including personal presentations to regulatory agencies of six countries. Member, FDA advisory panel. Recipient of Commissioner's Special Citation.

Authored or co-authored over 60 scientific publications; personally presented approximately 50 papers at scientific meetings.

Several concurrent academic appointments and seminars given at more than a dozen universities.

Currently Adjunct Professor of Biostatistics in the graduate faculty at The University of Texas School of Public Health and an independent consultant in the design, implementation and evaluation of clinical research programs in the pharmaceutical and biotechnology industries.

BR

Summary of Anticipated Expert Testimony

by

Dr. Bruce E. Rodda

The following is a summary of the anticipated expert testimony of Dr. Bruce E. Rodda in connection with the action entitled John Hancock Life Insurance Company, John Hancock Variable Life Insurance Company, and Manulife Insurance Company (f/k/a Investors Partner Insurance Company) v. Abbott Laboratories, U.S.D.C. (Mass.) Civil Action No. 05-11150-DPW. Dr. Rodda has been asked by Munger, Tolles & Olson LLP, on behalf of Abbott Laboratories, to provide the Court with expert testimony regarding the development of new pharmaceutical compounds, including without limitation, the statistical aspects of evaluating and interpreting the results of clinical trials in support of these developmental activities. Dr. Rodda's testimony may include, inter alia, expert testimony regarding the Abbott study referred to as ABT-Protocol M99-114, A Randomized, Double-Blind Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy.

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A summary of Dr. Rodda's training and experience can be found at pages 1-3 of

the Summary of Anticipated Expert Testimony by Dr. Bruce E. Rodda served on

plaintiffs on January 19, 2007.

This summary of Dr. Rodda's anticipated testimony is expected to include

opinions regarding the anticipated testimony of Dr. Barry Gold with regard to

statistical issues, the anticipated testimony of Dr. William Fairweather, the clinical

protocol and clinical study report for Abbott study ABT-M99-114, and various

statistical topics associated with clinical development generally and study ABT-

M99-114 in particular.

Dr. Rodda will testify based upon his own experience, using information and

materials available in the public domain (including, but not limited to, information

from the United States Food and Drug Administration's ("FDA") website and the

European Medicines Agency ("EMEA") website), and upon testimony and

materials obtained in discovery in this action. During his testimony, Dr. Rodda

may make reference to specific evidence contained in documents or witness

testimony.

The opinions and analysis contained in this summary of Dr. Rodda's anticipated

testimony are based on currently available information. Dr. Rodda's work is

continuing and he plans to analyze any new information. Dr. Rodda may modify

this summary in light of such new information. The present summary of Dr.

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Rodda's anticipated testimony may be supplemented by his deposition testimony.

Dr. Rodda is expected to opine on Dr. Gold's and Dr. Fairweather's anticipated testimony regarding the statistical considerations for Protocol M99-114 and the outcome of that study. He may opine on areas in which he feels either Dr. Gold's anticipated testimony or Dr. Fairweather's anticipated testimony is incorrect, incomplete, or unclear. Some of the comments that Dr. Rodda is expected to make in this regard are as follows.

Dr. Rodda's anticipated testimony may be grouped into three related areas -- general considerations, power and sample size considerations, and results and conclusions regarding Study M99-114.

GENERAL -- Dr. Rodda may opine that the underlying approach to designing and evaluating a comparative clinical trial is to assume, at the outset, that the treatments under investigation do not differ in their response. This is referred to in statistical terminology as the "null hypothesis". The study is then conducted with the objective of collecting information that will refute this hypothesis if the experimental treatment is, in fact, superior to the control treatment. If a substantial difference favoring the experimental treatment is observed when the study is completed, the conclusion would be that the experimental treatment is superior to the control. On the other hand, if a small difference was observed

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that was not inconsistent with the null hypothesis of no difference between the treatments under study, the conclusion would be that any real difference between the experimental and control treatments was too small to be of clinical importance.   In the context of Abbott study M99-114, this means that Abbott planned Study M99-114 with the expectation that ABT-594 was superior (and not equal) to placebo. Abbott designed Study M99-114 to have a high likelihood of producing results that would support the conclusion that ABT-594 was superior to placebo if, in fact, ABT-594 was truly superior. The results of M99-114 provided a substantial difference between each of the three doses of ABT-594 and placebo with respect to the primary variable (Likert pain scale), clearly confirming the superiority of each of the three doses of ABT-594 compared with placebo.

The results of a clinical trial are analyzed by statisticians to provide a basis for reaching conclusions. In his anticipated testimony (p. 15, line 16) Dr. Gold states that after data are "sorted into groups by dose and drug, one or more statistical tests will be applied." Dr. Rodda is expected to provide expert opinion that when the study is completed and the data have been unblinded, the statistical team will perform a complete statistical evaluation of the study results based on a statistical analysis plan (SAP) that was designed prior to unblinding the clinical data. This plan for the statistical analysis will sometimes be included in the body of the protocol or may be written as a standalone document for complex studies. If a standalone SAP is written, it is often appended to the protocol. The statistical

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analysis will be performed in concert with clinical experts and will be far more extensive than "one or more statistical tests".

With regard to Dr. Gold's anticipated testimony (page 5, line 4) Dr. Rodda may opine that Dr. Gold's use of the term "statistically evaluate" is unclear. Dr. Rodda is expected to discuss that while statistical concepts and techniques are important for the evaluation of safety and efficacy, there are other essential sources of input, e.g., clinical knowledge and experience that are essential in the evaluation of clinical trials.

POWER AND SAMPLE SIZE – Every clinical trial is different and the outcome of each clinical trial is unpredictable. If the identical trial were conducted many times, the results would differ each time for a variety of reasons. In addition to the uncertainty caused by random variation, other factors affect the confidence we have in the inferences made at the conclusion of a study. Some of these factors are the variability of the basic measurement, the size of the true difference between the experimental treatment and control (which is unknown and must be estimated from the study), the probability with which one wishes to detect a true difference if it exists (power), the risk one is prepared to take in declaring a true difference exists when it does not (Type I, or alpha, error), and the number of patients participating in the study.

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For example, to estimate the sample size for Protocol M99-114, Abbott used information from Protocol M98-833. That study suggested that a meaningful difference would be 11.4 units on a 100 point Likert scale with an associated standard deviation of 24.4 units, yielding a standardized difference (or treatment effect) of 0.46. Abbott utilized this standardized effect size, a power (or probability of getting a statistically significant outcome if the anticipated difference was real) of at least 0.8, and an acceptance of a 5% risk of falsely declaring ABT-594 superior to placebo, resulting in a planned sample size of approximately 80 patients in each group.

Dr. Rodda is also expected to testify that power is a concept that is only relevant for planning a clinical trial and is of little value in the interpretation of the results of a study.

Organizations sponsor clinical trials because they believe that their experimental treatment will have a clinically important difference over the standard treatment or a negative control. When a sponsor commits to performing a clinical trial, the sponsor wants to minimize the likelihood that the study will be inconclusive. Said differently, if the new treatment has a clinically important effect of Δ, the sponsor wants the study to have a high likelihood (or power) of demonstrating that effect with a "statistically significant" result. That is, the sponsor does not want the study to result in a conclusion of "ineffective" or "inconclusive" if the product really is superior to the control. Intuitively, because a larger trial provides more

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information than a similar smaller trial, a larger trial will be more likely to be conclusive than a smaller trial. Because clinical trials are very expensive, it is critical that studies be designed with the proper number of patients to satisfy their goals. Too many patients will result in unnecessary exposure of patients to experimental treatments and will be unnecessarily expensive. Too few patients, on the other hand, may result in an inconclusive study with the potential need to repeat it. For these reasons, a clear strategy must be followed for determining the number of patients required in a clinical trial.

Four basic factors influence the size of a clinical trial.

Variability – If an effect is associated with very small variability (i.e. the effect is very consistent), few subjects would need to be evaluated in a clinical trial to have confidence regarding any decisions made about the particular effect of interest. In contrast, if the effect is quite variable or inconsistent, conclusions based on the information provided by the same few patients would be less convincing. To provide the additional information necessary for similar confidence in the two cases, more patients must be evaluated when there is greater variability. For any scientific measure, precision increases and the likelihood of error decreases with additional information. In the clinical trial context, this information corresponds to a decrease in variability and/or an increase in the sample size.

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Clinically Important Difference between the Experimental and Control Treatment
- The second factor that influences the size of a study is the difference between the experimental treatment and the control that is clinically important. If the true (but unknown) difference between the comparative agents is very small, the study will require a large number of patients to provide adequate evidence to conclude that the specified difference is not zero as stated in the null hypothesis, but that a real difference exists between the treatments. On the other hand, if the sponsor believes that its new product is superior to the standard by a substantial margin, fewer patients will be required to obtain a statistically significant result if the true difference between the two treatments is large.

Risk of a False Positive Conclusion - The third consideration influencing the size of a clinical trial is the probability of falsely concluding the new treatment is superior when it is not. Consider that even if the experimental treatment and control treatment had inherently identical effects, the results of any specific study could randomly favor the experimental treatment to a degree that the (incorrect) conclusion would be that the experimental treatment is superior to the control treatment. This probability is also called a Type I error or alpha error (also referred to as the level of statistical significance) and is chosen before the study begins. At the conclusion of the study, the null hypothesis is tested against this alpha error standard (e.g. $p<0.05$), and if the results of the study are more extreme than would be expected if there were no true therapeutic difference, the result would be called "statistically significant (at the $p<0.05$ level)" and the

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conclusion would be that the experimental treatment is effective. The probability of making this conclusion in error would be 0.05 (or 1/20) in this example.

The Type I error is usually set at 0.05 (or 5%) and this is a standard recommended by the FDA and other regulatory agencies. Hypothesis tests routinely use this cutoff as the definition of "statistical significance". In the present study, the alpha level was chosen to be 0.05 and was specified in the protocol. At the conclusion of Study M99-114, the results of comparing each dose of ABT-594 with placebo were "statistically significant" ($p<0.05$), implying that each dose is truly superior to placebo with respect to pain.

Risk of a False Negative Conclusion/Power – It is also possible to incorrectly conclude that a clinically important effect is absent. Suppose that the experimental treatment is truly superior to the control treatment by, say Δ units. The results of any study are unpredictable, and even though the experimental treatment is, in fact, superior to the control treatment, the outcome of a particular study might result in a difference that was quite small, just by chance. In that case, the test of the null hypothesis would not be rejected (that is p would be greater than 0.05), and the incorrect conclusion would be that the experimental treatment is not superior to the control treatment. This type of error is referred to as Type II error or Beta error. The probability of correctly concluding that the experimental treatment is superior to the control is one minus the probability of incorrectly concluding the treatment is effective. The probability of correctly

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concluding the experimental treatment is superior is termed "power". Sponsors and investigators usually want this probability to be quite high and often select sample sizes that will provide 80% power. In study M99-114, the planned power was 80% power.

The relationships among the various factors contributing to the estimation of the sample size may be clearer by considering the following equation:

$$n = \frac{2(z_{\alpha/2} + z_\beta)^2 \sigma^2}{\Delta^2}$$

where: n is the sample size in each treatment group and

$z_{\alpha/2}$ is an index of the risk of a false positive --
the higher $z_{\alpha/2}$, the lower the risk (1.96 in Study M99-114)

z_β is an index of the risk of a false negative --
the higher z_β, the lower the risk (0.84 in Study M99-114)

σ is the standard deviation -- the measure of variability (σ = 24.4 from Study M98-833)

Δ is the difference the study is designed to detect (Δ=11.4 from Study M98-833) (Note that Δ/σ =0.46 is the standardized treatment effect Study M99-114 was designed to detect).

Note that the z-values above are values of standard normal deviates and are indexes of the probabilities; they do not represent the actual probabilities.

Dr. Rodda is expected to opine that the sample size for the Protocol M99-114 was estimated using a standard statistical approach for the comparison of two means. While there are usually several choices that may be appropriate for

estimating the sample size in any clinical trial, the procedures used in this study were consistent with good statistical practice and the sample size was appropriate for detecting the pre-specified standardized treatment effect of 0.46 in the primary variable with 80% power at an alpha level of 0.05.

It should be understood that just because a sample size has been chosen which appears to provide 80% power, it does not imply that there is an 80% chance that a given trial will be successful. Power is a concept that is only relevant for planning a clinical trial and is of little value in the interpretation of the results of a study.

Even if the planning has been appropriate and the calculations are correct consider the following points.

1. The assumptions used to estimate the sample size are approximations. The estimate of variability used in the calculation of sample size is derived from previous experience, often in a different environment than the given study. The variability that will actually occur in the planned study may be greater or less than used in the power calculations. In this case situation, the power would be lower or higher than anticipated.

2. The true difference between the treatments is unknown and the study may result in a higher or lower difference than that used to estimate the sample size.

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3. The new treatment may not actually be superior. (In fact, if a study correctly results in this conclusion, the study has not been a failure. The study has reached the correct conclusion, even though it was not the conclusion that was desired.)

4. Even if the new treatment is superior, the difference actually seen in a particular study may not be conclusive, just by chance.

Dr. Rodda will be prepared to discuss the concept of power as it relates to estimation of sample size and how this is a quantifiable risk chosen at the discretion of the sponsor. He will also be prepared to discuss the fact that neither "power", nor "statistical significance" is associated with the validity of a study. The validity of a study is dependent on its design and implementation. Two studies of the same design but of different sizes will both be equally valid if they are properly designed and executed. The larger study will provide more information and precision regarding the conclusions than the smaller study, but they can be equally valid.

In Dr. Gold's anticipated testimony (page 8, line1 and preceding), he states that variability is an important factor in the determination of the size of a study. Dr. Rodda is expected to opine that sample size is not determined solely by making certain assumptions about variability in the data. Sample size is also dependent

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on three other considerations as described previously: the risk (probability) of declaring an ineffective treatment to be effective at the conclusion of a study, the risk of not detecting a true clinically important difference at the conclusion of the study (and thereby erroneously concluding that an effective treatment is ineffective), and the magnitude of the clinically important treatment effect the study is designed to detect.

While Dr. Gold's contention (page 8, line 3) that the statistician's duties typically include estimating "very closely" how many patients must be enrolled, the term "very closely" is not correct.   Dr. Rodda is expected to opine that estimating sample size is dependent on both the clinically important difference and the estimated variability of response, in addition to the considerations regarding false positive and false negative errors presented previously.   The variability used in estimating a sample size is often an estimate from other studies and the estimated sample size is only as good as the estimate of the variability used to calculate it.

Beginning on page 8, line 5 of his anticipated testimony, Dr. Gold states that the "power of a study refers to the statistical test they have chosen and the probability that the test will fail to detect a true difference between two groups." Dr. Rodda is expected to opine that the "power" of the study is not only a function of the test to be used in the analysis of the primary variable, but more importantly, refers directly to the probability that the study, as designed, will find

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the pre-specified clinically important difference to be statistically significant at a pre-specified risk of a false positive outcome (declaring an ineffective drug to be effective). It is not, as Dr. Gold states, the probability of failing to detect a true, pre-specified, difference; it is the probability of actually detecting that difference. In addition, it is not the statistician who wishes to detect the difference; it is the sponsor, through the project team (and often following discussions with the FDA), who defines the pre-specified difference and is most interested in the outcome.

RESULTS AND CONCLUSIONS OF THE M99-114 STUDY– Dr. Rodda is also expected to testify that both the International Conference on Harmonization (ICH) and the U.S. Food and Drug Administration (FDA) recommend using as complete a dataset as possible for evaluating both safety and efficacy. Any patient that can be evaluated for efficacy should be included in the primary analysis. The analytic approach proposed for protocol for study M99-114 is consistent with the intent of this guidance. In fact, the protocol states that "all subjects receiving at least one dose of study drug with at least one diary-based baseline and at least one post-baseline pain assessment for the diary-based Pain Rating Scale will be included in the intent-to-treat analysis." The description of this dataset is included in the protocol and was defined before the study was begun. This dataset is consistent with ICH E-9 (Statistical Principles for Clinical Trials) which describes such a dataset as being "as complete as possible and as close as possible to the intention-to-treat ideal of including all randomized subjects." The clinical study report for Protocol M99-114 includes 225 of the 266 patients

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randomized to treatment in the primary efficacy analysis; all 266 patients are included in the safety analysis.

Patients withdraw from clinical trials for many reasons. Some are random and do not influence or bias the conclusions. However, patients may withdraw from clinical trials for two primary reasons that may be related to the treatment they receive - the adverse events they experience are such that they no longer wish to participate in the study or the treatment they are receiving is insufficiently effective to support their continued participation in the study. In either case, patients who withdraw from a study provide valuable information regarding the safety and efficacy of the product under investigation. Excluding patients from the analysis of clinical trials can substantially bias the conclusions reached. It is for this reason that both ICH guidelines and the FDA recommend using all patients with valuable data in the analysis of safety and efficacy. In reviewing the documentation of Abbott's deliberations prior to terminating enrollment, there was never a reference to using less than all evaluable patients in the appropriate analyses. Dr. Rodda may opine that given the above, Dr. Fairweather's position of considering only 137 patients for evaluation is scientifically inappropriate and inconsistent with ICH and FDA standards. To use only the 137 completing patients as Dr. Fairweather suggests would not be consistent with good scientific practice, would bias the results in favor of ABT-594, and would not be acceptable to the regulatory and scientific community.

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Documents relating to internal meetings at Abbott suggest that Abbott became aware at some point that they would not meet the enrollment goals in the planned enrollment period for Study M99-114. During the period preceding Abbott's decision to terminate enrollment, several activities took place in an effort to determine the impact of these factors on the probability that the study would satisfy its goal of distinguishing ABT-594 from placebo. In addition to efforts targeted at improving enrollment, Abbott evaluated the effect of smaller sample sizes on the probability (power) of detecting their predefined standardized treatment effect of 0.46. This was done in a fully blinded manner and assumed that all patients would be evaluable for efficacy. This activity focused on the following question: if the study concludes with a reduced number of patients, what is the probability (power) of detecting (finding statistically significant, $p < 0.05$) the proposed treatment effect of 0.46 between ABT-594 and Placebo? An example of the power considerations of this evaluation is contained in a memo from Mr. James Thomas to Ms. Rebecca L. Brown on 9/28/2000 in preparation for a meeting on the topic. This table is reproduced in part below.

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Option	Sample Size	Effect	Power
1	20	.46	0.29
2	25	.46	0.36
3	30	.46	0.42
4	35	.46	0.48
5	40	.46	0.53
6	45	.46	0.59
7	50	.46	0.62
8	55	.46	0.67
9	60	.46	0.71
10	65	.46	0.74
11	70	.46	0.77
12	75	.46	0.80
13	80	.46	0.82

Entries in this table include possible sample sizes (per group), the hypothesized treatment effect Study M99-114 was designed to detect and the power to detect this difference for each sample size. It can be seen from this table that the actual number of patients at the termination of enrollment (266 or about 65 per group) would provide 74% power to detect the hypothesized 0.46 treatment effect (compared with an initial power of at least 80% as cited in the protocol). This activity provided Abbott with a full understanding of the probabilities of Abbott's detecting their chosen effect for several smaller sample sizes. However, if the true treatment effect was larger than 0.46, the probability of finding this larger difference with the reduced sample size would increase.

It is common in clinical trials for actual enrollment to be less than planned. The only risk of stopping enrollment in a study with fewer patients than planned (as it relates to power) is that the treatment difference between the experimental agent and the control agent may not be statistically significant. In these cases, the

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sponsor may accept that the study's power to detect the originally hypothesized difference may be lower than used in estimating the study's size. There are several strategic considerations that may affect the sponsor's decision. Extending a study for an additional year, for example, to acquire the planned sample size may increase the cost to an unacceptable degree or expose the product to a new competitive agent such that the higher risk of extending the study may be unacceptable to the sponsor. In addition, after the study has begun, factors such as safety considerations with the new treatment or the introduction of a new competitor may require that a successful product possess a larger superiority over the control treatment than was originally planned. In this case, a reduced sample size may be consistent with a comparable, or perhaps greater, power than originally planned, since larger effects require smaller sample sizes.

Dr. Fairweather opined that of the 266 patients enrolled in this study, only 137 were "usable". This suggests that the remaining patients provided no information regarding the safety and efficacy of ABT-594. As stated earlier in this summary, those patients who withdraw from a clinical trial provide important information regarding the safety and efficacy of the products under study. ICH guidelines and the FDA would demand that all relevant information be used in the analysis; patients who withdraw cannot be considered "unusable" for either safety or efficacy. In addition, if one were to accept Dr. Fairweather's contention regarding usability, the original sample size of 320 patients would need to be increased by

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a factor of 266/137 (1.94), to a total enrollment of 621 patients to net 320 "usable" patients.

Dr. Rodda may opine that although Abbott terminated enrollment before reaching the target of 320 patients, Abbott carefully evaluated the possible outcomes of the study based on the reduced sample size and concluded that the reduced power associated with the originally hypothesized treatment effect was acceptable. Referring to the table above, Abbott knew that its power to detect their original hypothesized treatment effect of 0.46 would be approximately 74%, rather than the planned 80%. Viewed somewhat differently, while the initial plan had an 80% power to detect a treatment effect of 0.46, the actual intent-to-treat sample of 225 patients (Clinical Study Report, Table 11.4a) had an 80% power to detect a treatment effect of 0.56. Since the actual differences observed between the active treatment groups and the placebo group were all in the range of 0.8 to 0.9 units on the 11 point Likert scale (and were all statistically significant at the $p < 0.05$ level), the study clearly had adequate power to address the primary objective of the study, and the study should be considered conclusive (successful) in this respect.

Although Abbott did not know the margin by which ABT-594 would be superior to the control when Abbott decided to terminate enrollment in this study, that margin was substantially larger than originally anticipated. This difference was manifested in results that were statistically significant, rendering the question of

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adequate power (i.e. the probability of obtaining a statistically significant result) moot. Although both Dr. Gold and Dr. Fairweather had comments regarding the effective sample size of study M99-114, neither questioned that the study was conclusive in demonstrating that ABT-594 was superior to placebo with respect to the primary efficacy variable, despite a sample size that was somewhat less than originally planned.

References

1. European Medicines Agency: Scientific Guidelines for Human Medicinal Products: ICH E6 – Guideline for Good Clinical Practices. 1996.

2. European Medicines Agency: Scientific Guidelines for Human Medicinal Products: ICH E9 – Statistical Principles in Clinical Trials. 1998.

3. The World Medical Association: World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. 2004

4. 21 CFR 312.40 General requirements for use of an investigational new drug in a clinical investigation

5. Abbott communiqué Dr. James Thomas to Ms. Rebecca L. Brown – 9/28/2000

6. Summary of proposed expert testimony by Dr. Barry I. Gold

7. Summary of proposed expert testimony by Dr. William R. Fairweather

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Documents Reviewed by Dr. Bruce Rodda

Bates Nos.	Date	Description
-----	10/13/06	Expert report of Barry I. Gold
-----	01/19/07	Expert report of Dr. William R. Fairweather
-----	6/23/06	Supplemental Complaint
-----	2/6/06	Hancock's Objections & Responses to Abbott's First Set of Interrogatories
-----	9/27/06	Marilyn Collicott deposition transcript
ABBT 0004410-0004415	4/00/00	Collicott Exhibit 6
ABBT 0004436	8/00/00	Collicott Exhibit 10
ABBT 0004443-0004447	9/00/00	Collicott Exhibit 12
ABBT 0004448-0004454	10/00/00	Collicott Exhibit 15
ABBT 237155-237159	10/9/00	Collicott Exhibit 16
ABBT 0004455-0004459	11/00/00	Collicott Exhibit 17
ABBT 0004460-0004464	12/00/00	Collicott Exhibit 22
ABBT 0000322-0000327	1/00/01	Collicott Exhibit 27
ABBT 240624	1/8/01	Collicott Exhibit 28
ABBT 242693-242699	1/16/01	Collicott Exhibit 29
ABBT 0001748-0001758	4/23/01	Collicott Exhibit 39
ABBT 335154	5/4/01	Collicott Exhibit 41
ABBT 239029	5/18/01	Collicott Exhibit 42
ABBT 240374-240412	10/15/02	Collicott Exhibit 49
-----	9/29/06	Bruce McCarthy deposition transcript and all exhibits
ABBT 0020894-967	10/99/99	Draft 10/7/99 M99-114 Protocol
ABBT 0065818-0078893	-----	CD containing: Clinical Study Report and Clinical Protocol
-----	-----	CD containing: Amendment for Study M99-114
ABBT 159274	9/3/99	Email to Waleska from Siber
ABBT 51889	12/21/99	Email to Siebert from Thomas
ABBT 65818-65896	2/8/00	Protocol M99-114
ABBT 242154	5/25/00	Letter to Hoffstetter from Collicott
ABBT 33462-33467	5/31/00	Site breakdown/enrollment for M99-114
ABBT 79825-79826	6/20/00	Emails between Nunn and Thomas
ABBT 241296-241297	6/27/00	Emails among McCoy, Rowbotham and Collicott re barrier to enrollment
ABBT 161395	7/6/00	Email to Matalonis, et al from Garavalia
ABBT 82516	7/7/00	Email to Morris, et al from McCarthy
ABBT 239985-239988	7/10/00	Site breakdown/enrollment for M99-114
ABBT 83022	7/13/00	Email to Landsberg, et al from Collicott
ABBT 161644-161645	7/25/00	Emails among Biarnesen and Powers
ABBT 78935-78941	8/7/00	Email to Thomas from Hansen with patient listing
ABBT 335227-335307	8/23/00	ABT-594 Development Plan
ABBT 80232-80237	8/29/00	Email to Kacos from Thomas with data for power curves
ABBT 241302	8/31/00	Letter prototype to investigators from Collicott
ABBT 51907-51908	9/28/00	Power calculations

ABBT 82259	9/28/00	Email to Brown from Thomas with power calculations
ABBT 51892-51905	9/28/00	Email to Brown from Thomas with power calculations
ABBT 233741-233749	9/28/00	CT Recruitment and Centralized Screening Program
ABBT 237155-237159	10/9/00	Email to Nunn from Collicott with investigator tracking list
ABBT 107607-107609	10/30/00	Email to Biarnesen from Silber with list of project review questions
ABBT 109399-109400	11/22/00	Email to Morris from McCarthy with items for meeting discussion
ABBT 241843-241847	11/28/00	Email to Schanzenbach from Collicott
ABBT 81606	11/29/00	Email to Kacos from Thomas with confidence intervals for difference
ABBT 242373	12/6/00	Email to Biarnesen from Collicott re randomization goals
ABBT 233539-233540	12/14/00	Email to Schanzenbach from Collicott "decided to end enrollment as of 1/5/01
ABBT 240624	1/8/01	Email to Schanzenbach from Collicott
ABBT 81459-81460	1/12/01	Email to McCarthy from Thomas with adverse event experience
ABBT 233000	1/15/01	Email to Schanzenbach from Collicott
ABBT 242693-242699	1/16/01	Meeting agenda with tables of investigators and early terminations
ABBT 8169-8176	Feb 2001	Descriptive memo on marketing prospects
ABBT 246076-246084	Feb 2001	Descriptive memo on marketing prospects
ABBT 242650	2/5/01	Tracking report
ABBT 242503	2/12/01	Tracking report
ABBT 242681-242688	2/13/01	Meeting agenda with tables of investigators and early terminations
ABBT 237944	2/20/01	Tracking report
ABBT 233001	2/26/01	Email from Brownell to Collicott re tracking report
ABBT 238329-238335	2/27/01	Meeting handouts with tables of investigators and early terminations
ABBT 298380-298385	3/5/01	Meeting minutes: Pain Strategy Decision Analysis
ABBT 297530-297555	3/7/01	Abbott Portfolio Review
ABBT 238328	3/13/01	Tracking report
JH 8074-8211	3/13/01	Research Funding Agreement by Hancock and Abbott
ABBT 240978	3/20/01	Tracking report
ABBT 79111-79119	5/23/01	Adverse event experience tables
ABBT 241331-241560	7/31/01	M99-114 Analysis
ABBT 241298-241300	8/14/01	Study enrollment graphs
ABBT 80451	2/19/02	Email to Olson from Thomas "screening failure rate 47%"
ABBT 79395	3/6/02	Email to Biarnesen from Thomas indicating blind broken 4/23/01
ABBT 51885-51888	-----	Power curves
ABBT 155581-155587	-----	Initial Portfolio Prioritization

JH8153 – JH8210	February 2001	Descriptive Memoranda
ABBT0104016-0104017	11/21/00	Email from McCarthy to Silber
ABBT01214045-1214046	12/18/00	Email from Biamesen to Robinson
ABBT0122646-0122718	11/17/00	ABT-594 Project Review

CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 18, 2008.

Date: February 18, 2008.

<div align="right">

/s/ Eric J. Lorenzini
Eric J. Lorenzini (*pro hac vice*)

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